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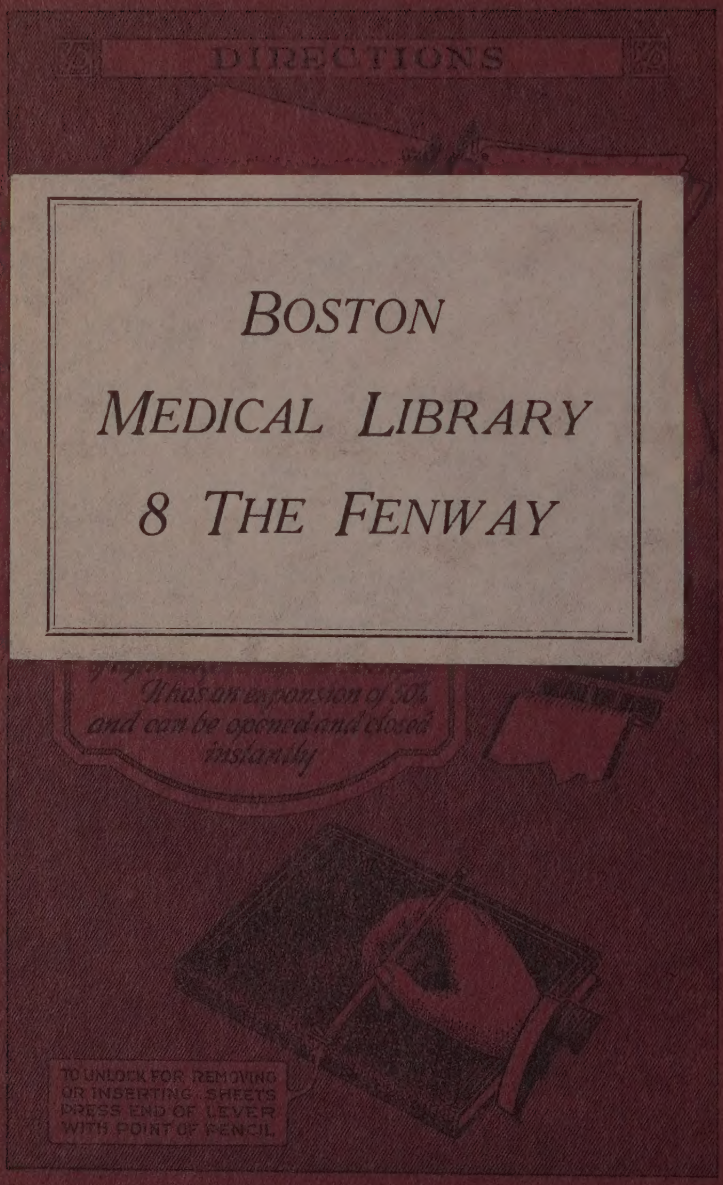

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EDITED BY HENRY A. CHRISTIAN, M.D., Sc.D., LL.D.

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VOLUME VII

The Diagnosis and Treatment of VARIATIONS IN BLOOD PRESSURE AND NEPHRITIS

By

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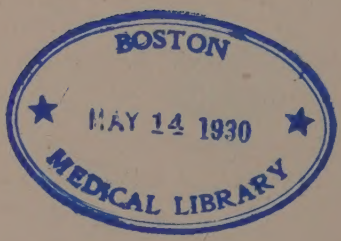

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TO

MY WIFE

JOHANNA KROEBER MOSENTHAL

PREFACE

A dual objective has been aimed at in this volume; first, a constructive summary of the reported facts and theories concerning blood pressure and nephritis, second, an interpretation of these.

The book was planned from the outset with the idea, so well expressed in the foreword by the editor, Professor Henry A. Christian, that the study of functional pathology (or pathological physiology) is of equal importance to that of morphological pathology. It is largely this point of view that distinguishes medical practice of today from that of thirty years ago.

Although this principle has been generally accepted in theory, it has not been put into actual practice as vigorously as it well might be. In some monographs on nephritis or Bright's disease the subject is frankly treated as centering about the anatomical changes in the kidneys, and all the functional disturbances are regarded as secondary to the renal involvement. In many other dissertations, while the theoretical approach is that Bright's disease is a constitutional affection, the practical application still adheres to the idea that the morphological pathology of the kidney is the main factor upon which the clinical and anatomical deviations from the normal necessarily depend. The conception of Bright's disease, as presented here, was not evolved for the production of this volume, but is the outgrowth of clinical experience, laboratory work and teaching.

It may not be out of place to mention a few points of what

has been stated in a general way. The conclusion is reached that there are several distinct types of elevated blood pressure: a classification of these is formulated: the view is expressed that increase in arterial tone is the functional disturbance responsible for essential hypertension and that peripheral vasoconstriction, usually thought of as the cause for an increased arterial tension, is in reality a secondary phenomenon in many instances of hypertension. The diseases associated with a permanently elevated blood pressure and those accompanying non-suppurative renal lesions have been grouped together as Bright's disease. The term nephritis has been reserved to designate the morphological pathology of the kidneys and nothing more than that. Bright's disease is described as a group of conditions in which six factors are concerned: nephritis (that is, the pathology of the kidney), renal function, edema, anemia, blood pressure and uremia. These occur, develop and recede with a certain degree of independence of one another and are, therefore, to be regarded as separate morbid processes; in many cases they coexist and form a disease complex; their interrelation is frequently puzzling, but sometimes it can be satisfactorily explained.

It is hoped that this book will constitute one step forward in establishing the various types of nephritis as part of constitutional affections, in which lesions of the kidney are of equal but of no greater importance than those in other organs and tissues.

The author desires to express his appreciation to Daniel R. Barr for the section on the Recording Sphygmomanometer, to Ernst P. Boas for the section on Capillary Pressure, to Harold M. Frost for the chapter on Blood Pressure As Related to Life Insurance, and to C. Ward Crampton, Edward C. Schneider and Harold M. Frost for an exposition of their functional effi-

ciency tests. Dr. Benjamin I. Ashe, Dr. S. Edward King and Dr. James J. Short have concentrated much of their energy during the past few years on the study of Bright's disease at the New York Post-Graduate Hospital. They have contributed the excellent chapters on anemia and on edema.

FOREWORD

To the man who practices medicine two questions arise with great frequency; what is the matter with my patient, and how shall I treat his ills? To answer these questions correctly is to practice medicine in a satisfactory manner. Consequently, diagnosis and treatment are of vital interest to every physician.

In the modern era of medicine very striking advances have been made in methods of diagnosis. Many new methods of precision have become available for bedside use. Discoveries in physics and chemistry have been applied in the clinic. Laboratory methods have been simplified so that they are available in diagnosis; many of them are such that they can be carried out readily by the physician himself. Older methods of examining the patient have been improved, and the implication of many signs long known are better understood. In utilizing these methods, even more than ever, is there need for clinical knowledge and judgment based on experience. The good diagnostician of today must know more facts, understand the use of more methods than was true of former generations of medical men.

For a time in recent progress in medicine it seemed as if advance in methods of treatment lagged behind advance in methods of diagnosis. There was a period of therapeutic nihilism. Many old methods of treatment had been discarded as better knowledge indicated their futility, and their place was not taken at once by more effective measures. In a period in which pathological anatomy dominated medicine, and particularly a post-mortem pathological anatomy, effectively to treat

many diseases seemed an impossibility. This period was followed by a newer pathology based more on a study of the living with advance in knowledge of function. Concepts of abnormal function stimulated renewed interest in methods of treatment. Great advances in our knowledge of etiology again brought improved methods of treatment along the lines of immunization, antitoxic sera, etc. Chemists developed a chemotherapy. Many new measures of applying physical methods in treatment were developed. A more rational basis for psychotherapy was evolved. From all of these changes there has come a present period of medicine in which treatment in all of its forms occupies possibly a larger place in medical literature than any other phase of medicine.

With so much known of diagnosis and treatment and with so many things being steadily added by medical investigators, there is a real need among those who practice medicine for comprehensive discussions of diagnosis and treatment by men competent to select what is best and to present it with sufficient detail and clarity for it to be of practical help in the problems of practice. For this purpose this series of "Monographs on Diagnosis and Treatment" has been prepared. Each volume is a complete discussion of the diagnosis and treatment of a certain group of diseases written by one author. The series is to be issued in loose-leaf form to make possible revisions and additions as new knowledge is available. It is offered with the hope that they, who read it, will be prepared to render to their patients a better service.

HENRY A. CHRISTIAN, *Editor.*

PETER BENT BRIGHAM HOSPITAL
Boston, Mass., March 9, 1928

PREFACE

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DIAGNOSIS AND TREATMENT OF VARIATIONS IN BLOOD PRESSURE AND NEPHRITIS

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CHAPTER I

PHYSIOLOGIC DYNAMICS CONTROLLING ARTERIAL PRESSURE

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INTRODUCTION

"That the blood exerts pressure upon the vessels through which it circulates is, of course, a necessary corollary of the fact that it flows; but more than a hundred years elapsed before Harvey's discovery of the circulation was followed by Hales' demonstration of the blood pressure, in 1733, and a second century before its accurate study was begun." (Theodore C. Janeway, the Clinical Study of Blood Pressure, 1904, page 3).

The pressure maintained in various parts of the circulatory system is spoken of as the arterial pressure, the venous pressure and the capillary pressure. It has become customary, in clinical medicine, to use the term "blood pressure" to mean the arterial pressure as measured in the brachial artery; the term hyper-

tension has come to mean a systolic blood pressure well above the average. Throughout this book these names are used in the sense that clinical usage has sanctioned. The so-called "systolic pressure" is the highest degree of pressure achieved in the arteries; this naturally follows on cardiac systole. The "diastolic pressure" is the lowest arterial pressure occurring during the cardiac cycle. The "pulse pressure" is the difference between the systolic and diastolic pressures.

The Circulatory System is Comparable to a Mechanical Apparatus only to a very Limited Degree

It is very tempting to explain the variations of blood pressure on the basis of a mechanical circulatory apparatus. The following table is furnished by Wiggers[1] and gives the results

Factors Affecting Blood Pressures

	Systolic Pressure	Diastolic Pressure	Pulse Pressure
Increased peripheral resistance	+	++	−
Decreased peripheral resistance	−	−−	+
Increased heart rate	+	++	−
Decreased heart rate	−	−−	+
Increased systolic discharge	++	+	+
Decreased systolic discharge	−−	−	−

Table 1. — Effect of factors affecting blood pressure regarded from the mechanical point of view (Wiggers).

that may be expected from a study of this sort. As Wiggers says, "The pressure within the arteries of an animal and in man does not vary in so simple a fashion as is indicated by an artificial circulation apparatus"; I have found this to be very true; during prolonged attempts to note the effect of increased or diminished heart rate on the blood pressure of my patients, I discovered that the blood pressure remained comparatively

stable in spite of the fact that the pulse might be fast or slow. On the other hand, in certain instances where the changes in the factors affecting blood pressure are very marked, as with the increased systolic discharge of blood in heart block, the compensating effort of the organism may fail and the theoretical

Stimulus	Effect		
	Cerebral Circulation	Peripheral Circulation	Heart Rate
Raising aortic pressure	Vessels dilated, B.P. lowered	Vessels dilated, B.P. lowered	Unchanged
Lowering aortic pressure	Vessels constricted, B.P. raised	Vessels constricted, B.P. raised	Unchanged
Lowering cerebral pressure	.....	Vessels constricted, B.P. raised	Increased
Raising cerebral pressure	.....	Vessels dilated, B.P. lowered	Slowed
Acute cerebral anemia	.....	Vessels constricted, B.P. raised	Slowed
Epinephrin in cerebral circulation	.....	Vessels dilated, B.P. lowered	Slowed
Epinephrin in systemic circulation	Vessels scarcely contracted, increased blood flow	Vessels strongly constricted, diminished blood flow	

TABLE 2. — Tabulation of the experimental results of Anrep and Starling. The far-reaching, compensatory effort to maintain the blood pressure as a whole at a constant level and to insure an adequate blood supply to all parts of the body is well illustrated.

mechanical effects upon the blood pressure may be realized. There is a compensatory mechanism occurring reflexly throughout the vascular system that tends to maintain a constant blood pressure in each person. These reflex paths must be extremely numerous and very ramifying; we know from some of the latest researches on these subjects not only that the smaller blood vessels of one organ contract and dilate independently, but that single arterioles and even capillaries may do this, as

has been shown for the kidneys, lungs, brain, muscle and possibly other tissues. The intricacies of the situation may be realized from the work of Anrep and Starling[2].

In the experiments, the results of which are summarized in Table 2, a crossed circulation was effected so that the head of one animal received its blood supply from the remainder of the body of another. In this way facts could be ascertained in regard to the influences of the systemic on the cerebral circulation and vice versa. It was found that the physiological effects were produced variously by stimulation of the vagus and vasomotor centres, and the vagus nerve and peripheral sympathetic nerve terminations.

It is interesting to note, in the results of Anrep and Starling[2], how the blood pressure in the aorta, brain and peripheral circulation do not rise and fall together but seem rather to compensate for one another, thus assuring an adequate blood supply to all regions of the body without excessive strain anywhere; nor does the heart rate in these experiments conform to the findings in the mechanical circulatory apparatus.

The above experiments show how complicated circulation is. Since our knowledge in this field is very limited, it is futile at present to attempt anything approaching a complete logical exposition of blood pressure phenomena in human beings. Therefore, the physician must accept blood pressure readings largely as empiric findings and allow explanations to await additional researches by physiologists. However, there are certain facts that deserve further consideration in connection with the blood pressure problem from the clinical point of view. It is on these facts, or findings, that the present therapy of hypertensive states is based, and they are the starting point for future progress.

The factors which are supposed to determine blood pressure have been tabulated time without number somewhat as follows:

A. Blood Volume.

B. Blood Viscosity.

C. Peripheral Resistance.

D. Pulse Volume — Cardiac Energy.

E. Elasticity of the Arterial Wall.

To these I should like to add one other, which appears to have been largely neglected, though, on theoretical grounds at least, it deserves careful consideration:

F. Arterial Tone.

Blood Volume

In theory, at least, an increase in blood volume would promote a rise in blood pressure. Keith, Rowntree and Geraghty[3] in the determination of blood volume in cases of hypertension could find no causal relationship between blood pressure and blood volume. In fact many of their hypertensive patients showed a small blood volume. On the other hand, in certain diseases blood volume and blood pressure run more or less parallel. Thus in pernicious anemia the blood pressure is low and hypertension, if present, disappears (Lerman and Means[4]) and the blood volume is diminished (Lindeman,[5] Denny[6]). In typical cases of polycythemia vera there is a parallel increase of blood pressure, blood viscosity and blood volume (Brown and Giffin[7]), although, as Weber[8] points out, the blood pressure in this disease may remain normal. The upshot of the problem in regard to the relation of blood pressure to blood volume is that, fundamentally, most of us believe that an increase in blood volume will effect a rise in blood pressure; from the practical

point of view apparently it is of comparatively little importance in the usual case of hypertension. It may, however, play a rôle in other conditions, as in pernicious anemia and polycythemia, although here blood viscosity and other factors would have to be reckoned with also. The relation of blood volume to salt metabolism is taken up in a subsequent section. The compensatory efforts on the part of the body to nullify the effects of an abnormal condition, like increased blood volume, also must be considered; in cases of polycythemia with increased blood volume, increased viscosity and a normal blood pressure, there is a vital balancing of forces that makes reasoning along purely mechanical lines valueless. This is illustrated very well in the effects of blood transfusion. I have observed several cases in which the transfusion of 1000 c.c. of blood brought about no rise in arterial pressure. Dr. Lester Unger, whose experience in this field is very great, tells me that this maintenance of an unchanged blood pressure after increased blood volume by transfusion, is the usual finding.

Blood Viscosity

Allbutt[9] says: "It is alleged that in the state of excessive blood pressure described independently by Huchard and myself in 1893–4 as precursory to arteriosclerosis and named by me hyperpiesis, by Huchard presclerosis, the viscosity of the blood is, or may be, raised; the observations on this point are, however, as yet too few and too lacking in authority to establish a rule." Somewhat later Lyon[10] in reviewing this subject concludes: "Viscosity of the blood is a very important factor in maintaining the blood pressure, but alterations in the thickness of the blood can be compensated for easily by the body, and hence only in exceptional cases (anemia and chronic venous

congestion with cyanosis) does an altered blood pressure manifest itself." This probably summarizes the question of the relation of blood viscosity and hypertension. In the usual case of clinical hypertension the blood viscosity is not altered. If it is changed, there is a tendency for other factors to compensate for this influence on the blood pressure. Thus a case of Bright's disease may exhibit hypertension in spite of an anemia with its attendant low blood viscosity. In polycythemia an increased blood viscosity may be considered as one of the reasons for an elevated blood pressure. In this connection a report of Patterson[11] is to the point: A case of polycythemia showing seven million red blood cells, 130 per cent. hemoglobin and a blood pressure of 204/120, had a lowering of blood pressure to 132/92, when the hemoglobin and red blood cells were reduced to normal by X-ray treatments to the long bones.

Peripheral Resistance

By "peripheral resistance" is meant the obstruction to the arterial flow in the smallest blood vessels that lie at the junction between the arteries and the capillaries. These are called the arterioles. The blood pressure in the larger arteries is more or less uniform; it is only when the arterioles are reached in the blood circuit that the tension diminishes to any extent, and it is principally at this point that the drop of about 50 mm. of mercury, which takes place between the arteries and veins, occurs.

The arterioles have the function of regulators of the blood flow to the capillaries. The arterial pressure is the reservoir of the potential energy which the arterioles may tap by dilating or limit by contracting. Such a control of blood flow according to the needs of a given area has been demonstrated beautifully by

Richards[12] and his associates for the afferent artery of the glomerulus in the kidney; similar changes, apparently, are found in other tissues, such as the voluntary muscle, the heart, the brain (Krogh[13], Wearn[14], Cobb and Talbott[15]) and probably throughout the body. The individual capillaries open and close intermittently and independently as well, but the main control of volume flow of blood is considered to be in the arterioles. Some very interesting facts which show that the arterioles have a "stop-cock" action have been brought out by Boas'[16, 17] observations that in the majority of cases of hypertension the capillary pressure is not higher than normal, and that the so-called capillary pulse is not produced in the capillaries at all but in the smaller arteries. Other factors that control blood pressure (cardiac output, arterial elasticity and tone) overcome this peripheral resistance to produce a flow of blood to the capillaries and veins, and thus arterial tension is maintained.

From this it may be gathered that under usual conditions (that is, if diseases producing changes in blood volume and viscosity, such as anemia and polycythemia, are excluded) the cardiac output, peripheral resistance and arterial tone constitute the active factors controlling blood pressure and are responsible for the characteristic variations in it; the elasticity of the arteries, as well as the blood viscosity and blood volume, remain as fixed influences not subject to appreciable change from week to week, much less from hour to hour or even minute to minute, and consequently are not responsible for the great fluctuations in the blood pressure that occur at times in every human being. Volhard[18] has gone so far as to say that in the causation of essential hypertension an increase of the peripheral resistance is the only deranged element of all those factors that are concerned in the production of arterial pressure.

Also Neuhof[19] in a carefully prepared and valuable essay says: "At least one positive statement may be made, namely, that pathological hypertension in its final analysis is due to contraction of the systemic arterioles and capillaries." This assumption is largely subscribed to at the present moment; it lacks experimental proof; its acceptance depends very largely on our conception of what "der Arterielle Hochdruck", or essential hypertension really is. This will be taken up in the section devoted to the different varieties or types of hypertension.

It may be sufficient to indicate here that excessive peripheral vasoconstriction, inducing peripheral resistance, may be local, as in Raynaud's disease, some instances of angina pectoris or intermittent claudication, or it may affect larger areas of the circulatory ramifications as presumably is the case in the vasomotor crises described by Pal[20] for lead poisoning, tabes dorsalis and nephritis. All the powers of the heart and the arteries, that are capable of controlling blood pressure, apparently are co-ordinated so as to maintain a flow of blood through the capillaries of each organ commensurate with its physiological needs; how ramifying these reflexes are may be gathered from Table 2.

When peripheral vessels become constricted, thus depriving the corresponding areas of their usual blood supply, there may be an increase in blood pressure to overcome this abnormal state. At least this is one of the explanations of the hypertension occurring in angina pectoris, nephritis and other conditions. Curiously enough, not every case of angina pectoris exhibits a hypertension during the attacks, nor does hypertension always accompany Bright's disease. Essential hypertension is generally believed to be due either to a general vasoconstriction brought on by some unknown functional disturbance, or such a vasoconstriction is considered to be the compensatory

effort of the pressor mechanism to overcome circulatory obstruction in the glomeruli of the kidney. These assumptions at present rest on theory only, and the author finds it impossible to agree fully with either idea. This matter will be taken up in greater detail in the section on varieties or types of hypertension.

Pulse Volume — Cardiac Energy

The minute volume of blood changes considerably with the amount of muscular activity and possibly also with other conditions. On passing from rest to exercise the circulatory rate doubled or trebled according to a man's physical training (Henderson, Haggard and Dolley[21]). Although blood pressure may increase with exercise, we know that it does not double or treble and rise from a normal of 120 systolic to 240 or 360. Consequently blood pressure is not directly proportional to the minute volume, although it bears some relation to it. Peripheral dilatation, allowing of a quicker emptying of the arterial bed, and relaxation of the arterial wall to accommodate a larger pulse volume may be the factors that compensate for the increased blood flow and prevent an inordinate rise of blood pressure. When hypertension exists, strenuous physical exercise may be detrimental because the increased minute flow cannot be handled without undue effect on a circulatory apparatus already laboring under a distinct handicap.

Clinically, the effect of an increased pulse volume may be noted in at least three conditions; heart block, aortic insufficiency and hyperthyroidism. Each of these has its own cause for the increased pulse volume and the consequent elevation of systolic pressure accompanied by low diastolic pressure. While it is not always true, in fact very far from it, the diagnosis of

aortic insufficiency or hyperthyroidism should be considered in every case whose pulse pressure is above 60; these conditions often are diagnosed readily, when they are particularly sought for, but overlooked easily unless especial attention is paid to their signs and symptoms. Hence a pulse pressure of 60 or higher may act as a useful reminder to search carefully for such lesions.

In heart block, with its very low pulse rate, the pulse volume must be increased correspondingly, inasmuch as the minute circulatory volume is probably maintained at its usual level. This yields the high pulse pressures, the result of an increased systolic with a normal diastolic tension, mentioned in the previous paragraph. Thus, in one of Read's[22] cases in which the pulse varied between 28 and 30, the blood pressures were 200/70 to 240/100, yielding a pulse pressure of 130 and higher. The high pulse volume producing the blood pressure characteristic of an overactive thyroid usually is ascribed to the demands of a high metabolic rate characteristic of this condition. The mechanical effects of aortic insufficiency upon blood pressure are obvious.

Marshall[23] has shown that the minute volume of the circulatory blood often remains constant whether the heart beat is fast or slow. Consequently the pulse volume, as well as the blood pressure, should vary inversely to the heart rate. This is theoretically true and applies to certain conditions, such as heart block, aortic insufficiency and hyperthyroidism; in many instances, however, it proves not to be the case, and other factors apparently compensate for the variation in cardiac rate and output and thus maintain the blood pressure at a more or less constant level. This may be observed frequently in many patients with variable pulse rates, but whose blood pressure

remains remarkably constant, not changing as might be ex-

Pulse Rate	Blood Pressure		Remarks
	Systolic	Diastolic	
72	210	150	
84	208	138	
96	198	148	
108	208	146	
170	202	148	Auricular tachycardia.

TABLE 3. — Illustration of the fact that one element that influences blood pressure may be compensated for by other factors. Note the variation of the pulse rate (and by inference changes in the cardiac output) in this man, age 47 years, while the blood pressure remains approximately constant. The above represents only a few observations of many; the days on which the pulse rate varied are the ones recorded.

pected from Table 1. An excellent example of this sort is given in Table 3.

That the force exerted by the heart muscle may be a factor in the production of blood pressure also should be kept in mind.

Blood Pressure		Remarks
Systolic	Diastolic	
224	140	Onset of uremic condition; blood pressure about at the
198	138	customary level for this patient.
204	140	
204	136	
194	122	
154	90	Three and half weeks later; moribund; blood pressure
154	88	maintained at a much lower level.
174	90	
138	80	
146	84	Death on this day.

TABLE 4. — Fall in blood pressure associated with loss of strength of the heart and other tissues in a moribund patient. This shows the futility of interpreting blood pressures as characteristic of a given disease during the last few days of life; it shows that in some instances a drop in blood pressure must be regarded as a poor prognostic sign, and finally it demonstrates how a weakened cardiac muscle may, in part at least, bring about a lowering of the arterial pressure. Data from a male nephritic, age 38.

The effect of lack of cardiac power may be noted often in moribund individuals in whom the arterial pressure frequently drops. Low pressures, under such circumstances, have been regarded many times as typical of the disease with which the patient is suffering, whereas in reality they are symptomatic of the diminishing vitality of the heart and other tissues. Such an instance is given in Table 4.

Another, though less common, example of a weakened heart muscle bringing about a fall in blood pressure is found in coronary thrombosis. However, no lowering of the blood pressure occurs if the occluded vessel is small or when the left ventricle is not involved. I am quoting the figures of Gager[24] (Table 5),

Before Coronary Occlusion	After Coronary Occlusion
156/92 – 166/108	98/78
170 – 240	110
150	90
200	120

TABLE 5. — Observations of Gager on the fall of blood pressure occurring with coronary thrombosis; there is no change in the pressure, if the left ventricle is not involved, or if the occluded vessel is a small one; from such results it may be concluded that weakness of the heart muscle will lower both the systolic and diastolic pressure levels.

although there are a considerable number of similar observations on this point. The drop of pressure so often noted in old people is presumably an indication of loss of cardiac power. This subject will be considered more fully under normal blood pressure in old age. Blood pressure may diminish from other causes than a weakened heart. However, when a distinct, persistent fall in tension takes place, it is necessary to consider this phase of the problem very seriously, for not uncommonly death follows within a week after such a drop in pressure although, at the moment, there may be a singular absence of signs pointing to

the precarious state of such patients. This is particularly true in old people.

Elasticity of the Arterial Wall

The arteries necessarily must distend to a considerable degree with each cardiac systole in order to accommodate the volume of blood forced into them. The arterial wall yields to the pressure within it and then contracts as the blood volume diminishes in the arterial system during diastole. In relating these phenomena to the elasticity of the arterial wall we imply that the elastic fibres in the wall of the blood vessels are mainly responsible for them. "The aorta with its well developed elastic coat acts specially as the reservoir of blood, the other vessels filling this function to a much less extent and to different degrees" (Norris, Bazett and McMillan[25]). This enables the aorta to supplement the propulsive force of the heart and provides a means of removing some of the circulatory strain from the more distal arteries. The importance of the aorta as a storage centre for the blood, analogous to the equalizing effect of a lake in a river system, as a regulator of the blood pressure, is shown in the reflexes recorded in the experiments of Anrep and Starling (Table 2). The importance of aortic disease, luetic aortitis, sclerosis, etc., must be recognized, therefore, as one of the pathological lesions that may have a far reaching influence upon blood pressure, though no very conclusive investigations upon this subject are, as yet, available.

The complexity of the subject, when an accurate evaluation is attempted of the factors entering into the elasticity of the arteries, is well stated by Norris, Bazett and McMillan[25]: "No simple relationships can, however, be expected in tubes with walls consisting partly of elastic tissue fibers, partly of muscle

fibers and partly of white fibrous tissue; probably the distensibility is slight when the white fibrous tissue carries the strain and much greater when the elastic fibers do so, while Hurthle's results suggest that the greatest variations in diameter with varying pressure may occur when the muscular coat is contracted and supporting the main strain." This gives the clue to the main changes taking place in the blood pressure as the result of variation in the elasticity of the arteries. The main point is that, in direct proportion as sclerosis occurs in the arteries with the consequent rigidity of their walls, the systolic pressure rises, the diastolic falls and the pulse pressure increases. How this takes place with advancing years, producing changes characteristic of the various decades of life, is discussed under normal blood pressure; the subject will be considered further under types of blood pressure.

Theoretically, when the elasticity of the arteries is normal, the cardiac output is accommodated with the least strain, and the blood flow to the capillaries is maintained at a constant rate. When elasticity is diminished, and the systolic pressure rises while the diastolic falls, we should expect these functions of the circulation (the accommodation of cardiac output and the constancy of capillary flow) to suffer. However, it is well known that such patients, as a rule, carry on very well, and that their outlook for a long life is good. This may be bound up with the fact that we are dealing largely with brain workers and might have an entirely different aspect, if subsistence was maintained more generally by physical exertion. Curiously enough, in hypertensive states, where the elasticity of the vessels remains normal or becomes exaggerated (see next section on arterial tone) and produces a high diastolic as well as a high systolic pressure, the prognosis, because of the

results of strain upon the heart and arteries, becomes much less favorable.

Arterial Tone

By this is meant the tonicity of the smooth muscle tissue in the arteries. There is a considerable amount of muscle in the arterial wall and presumably it must function. Yet in the literature and textbooks it is scarcely mentioned, and its action is practically ignored. However, if in hypertension an increase of diastolic pressure is maintained, there must be some force that brings it about, and this cannot conceivably be peripheral resistance alone but must, in addition, be an increased muscular tone of the arterial wall; this subject will be taken up in greater detail under the heading of types of hypertension.

Bibliography

1. Wiggers, C. J.: Modern Aspects of the Circulation in Health and Disease, Ed. 2, Lea & Febiger, Phila., 1923.
2. Anrep, G. V. and Starling, E. H.: Central and reflex regulation of the circulation, Proc. Roy. Soc., Sect. B., **97**: 463, 1924–25.
3. Keith, N. M., Rowntree, L. G. and Geraghty, J. T.: A method for the determination of plasma and blood volume, Arch. Int. Med., **16**: 547, 1915.
4. Lerman, J. and Means, J. H.: The blood pressure in pernicious anaemia, Am. Jour. Med. Sc., **175**: 777, 1928.
5. Lindeman, E.: The total blood volume in pernicious anaemia, Jour. Am. Med. Assoc., **70**: 1292, 1918.
6. Denny, G. P.: Blood volume in pernicious anaemia, Arch. Int. Med., **27**: 38, 1921.
7. Brown, G. E. and Giffin, H. Z.: Capillaries and blood volume in polycythemia vera, Am. Jour. Med. Sc., **166**: 489, 1923.
8. Weber, F. P.: Polycythemia hypertonica; is polycythemia a somewhat favorable sign in high blood pressure cases? Brit. Med. Jour., **2**: 98, 1927.
9. Allbutt, C.: The viscosity of the blood, Quart. Jour. Med., **4**: 342, 1911.

10. Lyon, D. M.: Blood viscosity and blood pressure, Quart. Jour. Med., **14**: 398, 1921.
11. Patterson, S. W.: Polycythemia rubra relieved by X-ray treatment, Lancet, **2**: 1112, 1925.
12. Richards, A. N.: Nature and mode of regulation of glomerular function, Am. Jour. Med. Sc., **170**: 781, 1925.
13. Krogh, August: The Anatomy and Physiology of Capillaries, Yale University Press, 1924.
14. Wearn, J. T.: Studies of the capillaries and Thebesian vessels of human and cat hearts, Jour. Clin. Invest., Proceedings of 17th Meeting, 572, 1924–25.
15. Cobb, S. and Talbott, J. H.: Studies in cerebral circulation: a quantitative study of cerebral capillaries, Trans. Assoc. Am. Phys., **42**: 255, 1927.
16. Boas, E. P. and Frant, S.: The capillary blood pressure in arterial hypertension, Arch. Int. Med., **30**: 40, 1922.
17. Boas, E. P.: Nature of the so-called capillary pulse, Arch. Int. Med., **29**: 763, 1922.
18. Volhard, F.: Der Arterielle Hochdruck, Verhandlungen d. Deutschen Gesellschaft f. innere Medizin, **25**: 134, 1923.
19. Neuhof, S.: Problems in hypertension — an attempt to correlate hypothetical and practical considerations, Am. Jour. Med. Sc., **168**: 668, 1924.
20. Pal, J.: Gefässkrisen, S. Hirzel, Leipzig, 1905.
21. Henderson, Y., Haggard, H. W. and Dolley, F. S.: The efficiency of the heart and the significance of rapid and slow pulse rates, Am. Jour. Physiol., **82**: 512, 1927.
22. Read, J. M.: Pulse pressure, its probable relationship to stroke volume, Proc. Soc. Exp. Biol. and Med., **24**: 564, 1927.
23. Marshall, E. K., Jr.: Studies on the cardiac output of the dog, Jour. Pharm. and Exp. Therap., **29**: 167, 1926.
24. Gager, L. T.: Blood pressure changes accompanying coronary occlusion, Jour. Am. Med. Assoc., **84**: 1730, 1925.
25. Norris, G. W., Bazett, H. C. and McMillan, T. M.: Blood Pressure, its Clinical Applications, Lea & Febiger, Phila., 1927.

CHAPTER II

NORMAL ARTERIAL PRESSURE

Average normal blood pressure values are now available in almost limitless numbers. They agree closely on the whole, but the diastolic readings in the various tables differ by as much as ten points in some instances, thus indicating that the criteria for estimating diastolic blood pressure are either not established firmly or admit of various interpretations. However, because of the general agreement, only one set of observations is presented here to cover each age.

In children (see Table 6) it is readily noted that the systolic

Age	*Systolic Pressure*	*Diastolic Pressure*	*Pulse Pressure*
3	91.8	65.6	26.2
4	91.6	64.9	26.7
5	91.3	64.4	26.9
6	92.6	67.3	25.3
7	94.0	66.3	27.7
8	93.6	64.7	28.9
9	94.3	71.0	23.3
10	99.2	67.1	32.1
11	97.1	65.5	31.6
12	102.3	65.2	37.1
13	103.6	70.5	33.1
14	106.1	67.4	38.7
15	105.6	67.5	38.1

TABLE 6. — Blood pressure in normal children (Judson and Nicholson)[1].

pressure is very low (about 92 mm. Hg. at age 3 to 6 years) and increases up to age 20 (see Table 7) when it reaches a level of 120. The diastolic pressure does not rise proportionately. Compared to a systolic increase of about 28 mm. Hg. during

these years, the diastolic values advance only 14 points. Consequently, the pulse pressure is extremely low in childhood and rises up to about age 20. From 20 to 40, as shown in Table 7, the blood pressures remain fairly constant. Then a further

Age	*Systolic Pressure*	*Diastolic Pressure*	*Pulse Pressure*
10	103	70	33
15	113	75	38
20	120	80	40
25	122	81	41
30	123	82	41
35	124	83	41
40	126	84	42
45	128	85	43
50	130	86	44
55	132	87	45
60	135	89	46

TABLE 7. — Average normal blood pressure according to Arthur Hunter[2] in approximately a quarter of a million healthy individuals.

rise occurs, paralleling the change occurring in the period from early childhood to maturity, namely, the disproportionately greater increase of systolic as compared to the diastolic pressure. The figures given in these tables speak for themselves as to the average values of the blood pressure readings.

Age	*Number Examined*	*Systolic Pressure*	*Diastolic Pressure*	*Pulse Pressure*
65–69	32	151	82	65
70–74	39	160	86	73
75–79	38	166	86	79
80–84	27	175	84	83
85–89	7	170	90	77
90–94	7	142	81	61

TABLE 8. — Blood pressure readings in men and women age 65 to 94 according to Bowes[3].

With the advent of old age (see Table 8) there is a sharp rise in systolic pressure, the diastolic scarcely changing at all. With extreme old age the systolic pressure becomes lower. As a complement to these figures, the pulse pressure in old age

reaches a level of about 80 mm. Hg., a point which in younger years would be decidedly pathological. The rise of blood pressure with advancing years may be regarded either as a sign of physical deterioration or simply as the physiological expression of growing old. In either event, one may consider the average blood pressure of about 120/80 at the age 20 to 40 as the expression of conditions before the processes characteristic of older years become evident. The explanation that has been offered generally for the rise of systolic pressure and the less marked elevation of the diastolic pressure coming on with more or less regularity from infancy to old age, is that through the progressive increase of connective tissue in the arteries, that is, an arteriosclerosis, the blood vessels tend to lose their elasticity and approach, to a greater or less degree, the state of rigid tubes. An absolutely unyielding, stiff-walled arterial system would bring about an enormous rise in systolic pressure and a lowering of diastolic tension to the vanishing point. Such extreme changes of course are only approached but never realized, because even in advanced conditions some part of the arterial tree always maintains its elasticity. The blood pressures in older people, as will be shown a little further on, show much more variation from the average figures than in younger individuals; this may be ascribed to the fact that arteriosclerosis develops rapidly in some, whereas it may be scarcely manifest in others.

The preceding table (7) of young and middle-aged adults, based on life insurance observations, presumably represents men almost to the exclusion of women. When blood pressure readings on women and men are taken up separately (see Table 9), it becomes very evident that the blood pressure in women, after the menopause, increases much more rapidly. This difference

appears to be very marked and again shows the same tendency of rising blood pressure previously noted, namely, that the systolic pressure increases more than the diastolic, thus bringing about a distinct elevation in the pulse pressure. David Riesman[5], some time ago, noted this association of hypertension and menopause. Saller, from whom this table (9) is taken, also

Age Years	Men			Women		
	Systolic Pressure	Diastolic Pressure	Pulse Pressure	Systolic Pressure	Diastolic Pressure	Pulse Pressure
18–20	117	69	48	118	69	49
21–23	120	72	48	120	70	50
24–26	122	71	51	118	72	46
27–29	120	72	48	120	74	46
30–32	121	72	49	120	74	46
33–35	120	73	47	119	73	46
36–38	120	74	46	123	76	47
39–41	123	74	49	124	76	48
42–44	122	75	47	127	78	49
45–47	121	74	47	135	79	56
48–50	124	76	48	142	80	62
51–53	126	75	51	148	85	63
54–56	127	76	51	148	89	59
57–59	129	76	53	152	87	65
60–67	133	77	56	159	88	71
68–89	136	78	58	167	89	78

TABLE 9. — Blood pressure readings in more than 4000 men and women, at various ages, adapted from Saller[4]; in men after 50 and in women after the menopause the blood pressure rises; this rise is greater in the systolic than the diastolic and consequently the pulse pressure increases; in women these changes are more pronounced than in men.

supposes that the menopause is responsible for his findings. Alvarez and Zimmermann[6] believe that the blood pressure in women is in inverse proportion to ovarian activity, and Alvarez, Wilson and Mahoney[7] consider it likely that a tendency to hypertension is suppressed in women so long as the ovaries function well.

It must be understood distinctly that the above tables state average determinations and nothing more and nothing less. They set forth readings on a great many individuals and may be regarded as representative figures as far as averages are concerned. However, they do not give us the possible variations within normal limits that blood pressure readings may assume. Consequently, it has become customary to regard all blood pressure readings above 140 systolic in adults as abnormal and portending evil effects from cardio-vascular strain. There are individuals who normally exhibit a blood pressure above the average; such records are given in Tables 10 and 11. In both

Date	Blood Pressure		Pulse Pressure
	Systolic	Diastolic	
1923, Jan. 23	149	81	68
May 28	139	86	53
1924, Feb. 4	140	84	56
Oct. 3	138	70	68
1925, Jan. 7	132	78	54
Aug. 3	126	84	42
1926, Jan. 20	128	84	44
Nov. 26	146	82	64
1927, Mar. 23	144	86	58
July 21	140	84	56
1928, Feb. 23	132	90	42
Mar. 9	148	78	70

TABLE 10. — L. J. M., a man, aged 33 had a blood pressure constantly above normal; the readings did not rise in the course of five years. Attention is called to the high pulse pressure. In February, 1928, definite signs of hyperthyroidism developed (basal metabolic rate, plus 24 per cent.) (Mosenthal)[8].

of these instances an elevated blood pressure, according to the usual normal standards, was present over a number of years, in one case for 16 years and possibly longer. In the captions an attempt is made to explain these pressures on pathological physiological grounds. However, there are many instances,

as even in the present ones, where such explanations may not cover the situation entirely. These cases of elevated blood pressure, regarded as the expression of a normal cardio-vascular system, have one characteristic that differentiates them from the actual case of essential hypertension. This is the fact that in them the blood pressure remains constant, or relatively so, while in pathological hypertension the blood pressure usually tends to climb to higher levels from year to year. This is very

Date	Blood Pressure		Date	Blood Pressure	
	Systolic	Diastolic		Systolic	Diastolic
1912.....	145		1923, July.....	140	96
1917.....	142	98	1924, January...	148	98
1919, February...	142	96	October...	148	100
December ..	152	98	1925, March....	140	92
1920, June.....	154	100	November.	152	100
December ..	142	100	1926, April	152	102
1921, August.....	158	104	July.....	146	97
December ..	142	98	1927, January...	142	98
1922, September..	140	90	October...	154	102
November..	150	96	1928, April.....	142	101
1923, May.....	160	100	May.....	154	100

TABLE 11. — In a man, aged 50, the blood pressure was constantly high for no apparent reason; there was a tendency to overweight, though the blood pressure remained constant whether the weight was normal or 30 pounds (13.6 Kg.) above normal. Hyperglycemia was present. The highest and lowest blood pressure readings of each year are recorded (Mosenthal)[8].

well shown in Table 12. How to differentiate these cases, the normal person with a blood pressure higher than the average from the individual with essential hypertension, it is impossible to state definitely. Only by constantly repeated blood pressure readings can the diagnosis be made. It is important to carry these out, as elevated systolic blood pressures below 170 mm., even if continuing for a long time, will not bring about any great degree of damage. This, at least, has been my experience.

It is interesting to note a statement of J. W. Fischer[5], which has a distinct bearing on the idea that a blood pressure, elevated above the average normal, is not necessarily a bad prognostic sign or an indication of disease: "It might be well to state that, where an applicant (for life insurance) was reported as having a high blood pressure with no other impairment, was rejected by the company, and after varied subsequent treatment (correction

Date	Blood Pressure		Date	Blood Pressure	
	Systolic	Diastolic		Systolic	Diastolic
1919, Nov. 8.....	158	110	1924, April 9....	158	124
1920, June 6.....	146	98	June 6....	176	118
Dec. 3.....	150	110	Nov. 10...	182	120
1921, Mar. 25....	154	106	1925, April 6....	188	132
Sept. 27....	156	119	Aug. 10 ...	194	130
Dec. 10.....	170	120	Dec. 23 ...	198	146
1922, Feb. 27.....	158	106	1926, Jan. 9.....	203	154
Sept. 29....	178	130	Mar. 8....	202	134
Dec. 16.....	165	124	Nov. 3....	196	128
1923, Feb. 15.....	171	129	1927, Jan. 13....	204	148
Sept. 4.....	168	117	July 18....	185	144
Dec. 8.....	174	126	Sept. 21...	210	150
			Nov. 11...	178	123

TABLE 12. — Y., a man, aged 40, in 1920, showed a constantly rising blood pressure in spite of various forms of treatment, including adequate rest, lessened responsibilities, good hygiene and various other measures (Mosenthal)[8].

in diet, change in mode of living, proper exercise, etc.) the blood pressure became normal and insurance was granted in this and other companies, the hypertension having been proved to be temporary or accidental, such cases were not included in our study of risks rejected. We did, however, obtain our mortality upon this class of risks, accepted by the company as standard risks, and the mortality was found to be favorable as compared with the general mortality of the company."

This leads to the consideration of what figures should be

regarded as constituting the outside limitations of the normal. The following two tables (tables 13 and 14), taken from Saller[4] and Stocks and Karn[10], bear on this point. According to these authors

Age Years	*Systolic Blood Pressure*	
	Men	*Women*
21–35	98–144	99–138
35–47		100–155
48–53	96–154	100–190
54–59	97–159	104–196
60–67	93–173	102–216
68–89	86–186	112–222

TABLE 13. — Upper and lower limits for normal blood pressure in men and women at different ages, as suggested by Saller[4].

Central Ages	Outside these limits pressures are almost certainly pathological	
	Systolic	Diastolic
7	59–128	34–86
8	62–131	35–85
9	66–135	36–88
10	69–138	38–90
11	72–141	40–92
12	75–144	42–94
13	80–149	45–97
14	84–153	47–99
15	89–158	49–101
16	93–162	51–103
17	95–165	52–104
18	97–166	54–106
19	.....	57–109
20–24	98–167	59–111
25–29		58–110
30–40		55–107

TABLE 14. — Probable limits of normality in blood pressure readings at various ages (Stocks and Karn)[10].

there are normal blood pressures outside of the limits of the average blood pressure readings; furthermore they believe that the variation in possible normal pressures is wide. The data which they furnished express this idea most forcibly. The author is in

thorough accord with these conclusions, and attention may again be called to the three cases cited above. In two of these the blood pressure is distinctly above the average but appeared to be normal for the particular individuals and without any evil consequences. On the other hand, the case that subsequently developed a marked hypertension shows with what circumspection we must enter upon an analysis of such variations from the normal.

In old age, such variations in arterial tension are exceedingly marked. Table 15 from Thompson and Todd[11] serves to make this clear.

Systolic Pressure mm. Hg.	No.	Diastolic Pressure mm. Hg.	No.	Pulse Pressure mm. Hg.	No.
0–129	18	0–29	3	30–49	8
130–149	31	30–49	0	50–69	35
150–169	23	50–69	22	70–89	32
170–189	20	70–89	54	90–109	17
190–209	7	90–109	21	110–129	7
210–229	1	110–129	2	130–149	2
230–249	2	.....		150–169	0
				170–189	1

TABLE 15. — Blood pressure observations in men age 75 to 92 according to Thompson and Todd[11]. These figures show how impractical it is to speak of a normal average blood pressure in people of advancing years; apparently there is a characteristic blood pressure which each individual acquires as he grows older. This may be considered the physiological expression of the changes that occur in the cardio-vascular system of each person.

In this table the blood pressure in old people is shown to vary from normal to 249 systolic, and from normal, or below normal, to 129 diastolic. Thompson and Todd believe all these cases to be normal for their age and consider that these variations of blood pressure in persons above 75 are to be considered as the physiological expression of the changes that occur in the cardio-vascular system of each individual.

The great differences between the blood pressure readings of the young adult and the old individual have been ascribed to the increasing rigidity of the arteries. The blood pressure changes naturally might be expected to occur in direct proportion to the advancing arteriosclerosis. Since this degenerative process varies in each individual, one should expect the blood pressures of older people to show deviations from the average. Practically all authors, describing blood pressure changes in old age, agree that the very high systolic pressures are very well taken care of, and that these cases show no symptoms referable to the hypertension. This may be due to the fact that, while the diastolic pressure remains comparatively low, only a moderate burden is thrown upon the heart. A further point worth mentioning in regard to the blood pressure in old age is that, where the heart muscle becomes deficient in its power, the systolic pressure drops to a remarkable extent, and the pulse pressure becomes very low. With proper cardiac treatment this condition may be remedied readily. A considerable fall in systolic pressure accompanied by a lowering of the pulse pressure, in an old person, should be regarded as a signal that the heart is not functioning adequately.

Bibliography

1. Judson, C. F. and Nicholson, P.: Blood pressure in normal children, Am. Jour. Dis. Child., **8**: 257, 1914.
2. Hunter, Arthur W.: Blood pressure; what affects it? An address before Association of Life Insurance Presidents.
3. Bowes, L. M.: Blood pressure in the aged, Jour. Lab. and Clin. Med., **2**: 256, 1917.
4. Saller, K.: Über die Altersveränderungen des Blutdrucks, Ztschr. f. d. ges. exper. Med., **58**: 683, 1928.
5. Riesman, David: Hypertension in women, Jour. Am. Med. Assoc., **73**: 330, 1919.

6. Alvarez, W. C., and Zimmerman, A.: Blood pressure in women as influenced by sexual organs, Arch. Int. Med., **37**: 597, 1926.
7. Alvarez, W. C., Wilson, R. and Mahoney, L. J.: Blood pressures in 15,000 university freshmen, Arch. Int. Med., **32**: 17, 1923.
8. Mosenthal, H. O.: Treatment of essential hypertension, Jour. Am. Med. Assoc., **91**: 698, 1928.
9. Fischer, J. W.: The diagnostic value of the use of the sphygmomanometer in the examinations for life insurance, Proc. Life Insurance Medical Directors.
10. Stocks, Percy and Karn, M. Noel: Blood Pressure in Early Life a Statistical Study, Cambridge University Press, London, 1924.
11. Thompson, R. Y. C. and Todd, R. E.: Old age and blood pressure problems, Lancet, **2**: 503, 1922.

CHAPTER III

CLINICAL METHODS OF ESTIMATING BLOOD PRESSURE

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Most sphygmomanometers on the market, whether of the mercury or aneroid type, are satisfactory. The standard of measurement is the height in millimeters of a mercury column required to equal the blood pressure. A warning against too small an arm band, which does not correct for the compression of the soft tissues, seems scarcely necessary today, as practically all makers equip their instruments with an arm band at least 12 centimeters in width. Three methods of determining blood pressure, the visual, the palpatory and the auscultatory, are used.

Visual Method

Of these, the visual method, is almost never used, and its only value may be said to be as a check to the auscultatory procedure. After the brachial artery is compressed by inflation of the arm band, and the air is allowed to escape slowly out of the circuit, the first vibration of the mercury column or needle indicates the systolic pressure; the point of maximal oscillations

corresponds to the diastolic reading. It is remarkable how closely some of the observers in the past were able to gage these signals that today are considered to be too inaccurate for conclusive blood pressure estimations.

Palpatory Method

One of the earliest successful methods of blood pressure determination was that obtained by palpating the radial artery, while the corresponding brachial artery was compressed by the inflated cuff. After the pulse has been obliterated completely and the pressure within the manometer circuit gradually released, the pressure at which the radial pulsation first returns is read as the systolic pressure. This method is still used and is of obvious value when a stethoscope is not at hand; it is also extremely serviceable as a routine check to the auscultatory

Observer	Subjects	Difference in systolic reading between palpatory and auscultatory method
Stocks and Karn	Boys age 5	2.7 mm. increasing with age to:
	Boys age 15.5	14.2 mm.
Korotkoff	Mostly adults	10–12 mm.
Gittings	" "	16.7 mm.
Warfield	" "	6–14 mm.
Prendergast	" "	5–10 mm.
Swan	" "	10 mm.
Kilgore	Adult males	12.7 mm.

Table 16. — Findings, according to Stocks and Karn[1], showing the difference between the palpatory and auscultatory methods in determining systolic blood pressure; the auscultatory method gives the higher readings.

method, or when the stethoscope does not give clear results, and there are many such instances. It is believed generally that the systolic pressure as obtained by palpation is about 5 to 10 mm. of mercury lower than the figures derived from auscul-

tatory observation; this is approximately correct. Stocks and Karn[1], from their observations on 250 boys and from a survey of the literature, which they quote, formulate the table on the opposite page (table 16).

From the above data, Stocks and Karn conclude that "13–14 mm. is a fair estimate of the mean correction which should be applied to palpatory readings of systolic pressure in normal young male adults, whilst for boys the difference is progressively smaller with decreasing age to about 3 mm. at age 7."

Auscultatory Method

This was first described by Korotkoff[2] in 1905 and has become the method of choice. It is easy to carry out and furnishes the clinician with the only accurate means at his command of estimating the diastolic pressure, which is gradually becoming more and more important in the diagnosis and prognosis of abnormal blood pressure states.

The cuff is applied over the brachial artery above the bend of the elbow; care must be taken that the part of the cuff which will exert the pressure when inflated covers the brachial artery adequately; this may seem a superfluous suggestion but I have often seen nurses and physicians, both young and old, apply the armlet in such a fashion that the gap between its ends is the part that is applied over the blood vessel. For quick accurate readings it is best to palpate the blood vessels at the bend of the elbow; the one on the inner side usually beats more forcibly; the stethoscope then is placed over this artery. It has become customary to prefer the Bowles type for this purpose. The bell of this stethoscope covers a large surface, and therefore, makes it comparatively easy to come in contact with

the artery. However, it has been my experience, especially when the sounds are difficult to hear and decipher, that the ordinary bell type of instrument, when placed accurately over the artery, yields results that are interpreted much more readily. The manometer circuit is inflated rapidly until all the sounds disappear, and the radial pulse becomes obliterated, and then the pressure is released gradually. Now a series of sounds is heard that has been divided usually into four phases as follows:

Phase	Characterized by	Significance
1	Sharp tapping sounds	The first appearance of the sound marks the systolic pressure
2	Murmurs or disappearance of all sounds	
3	Sharp tapping sounds	The termination of phase 3, when the sharp sounds cease is the diastolic pressure
4	Muffled sounds lapsing into silence	

There are several points worth bearing in mind when carrying out the auscultatory method:

Phases 1 and 2 may repeat themselves, that is, the sharp sounds may be heard and then disappear only to be succeeded by another cycle of sounds and silence, before the clear sounds of phase 3 become established. The result often is that the second cycle of phase 1, if we can call it such, is interpreted as being the systolic pressure. I know one case in which two of us for a period of months consistently interpreted a systolic reading to be about 180 when in reality it was in the neighborhood of 220, as subsequent observations showed. By checking the systolic auscultatory reading by palpation of the radial pulse this error can be avoided. As far as the author knows, there has been no satisfactory explanation of this repetition of phases 1 and 2. This phenomenon was first described by Cook and

Taussig in 1917. It has been termed the "silent gap" by Gibson[3] and the "auscultatory gap" by Mudd and White[4].

Phase 3 may continue to the zero point on the manometer; such a diastolic reading may have some justification in marked aortic insufficiency but certainly not in persons with a normal cardiac mechanism, and yet it is found occasionally. Such readings simply have to be discounted.

Great care must be taken that the termination of phase 3, i.e., the point at which the sharp sounds cease, marks the diastolic pressure. Formerly, the disappearance of all sounds was regarded by many as the proper point to take this reading; however, the researches of Warfield[5] and others have established definitely the fact that the proper pressure level at which the diastolic reading should be made is at the end of phase 3, when the sharp sounds cease and the muffled sounds begin. In Warfield's own words this very important fact is stated: "— the point where diastolic pressure should be read is at the tone change from clear to dull, not at the point where all sound disappears. This is, as a rule, an appreciable interval below diastolic pressure. In man this point where diastolic pressure should be read is just at the point where the third clear tone phase suddenly becomes a dull sound."

Recording Sphygmomanometer *

Daniel R. Barr

"The desirability of automatically recording blood pressure in clinic routine has long been recognized, and with the advent of the new Tycos recording sphygmomanometer this seems at last to have become entirely practicable.

* Reprinted by courtesy of American Medical Association.

"The latest development in the mechanical determinaton of blood pressure enables one to do away entirely with the stethoscope, palpating finger and indicating hand, thus eliminating completely the personal equation, and further gives a permanent record of unquestioned accuracy. Its service to the anesthetist, surgeon, diagnostician and general practitioner is well nigh incalculable, as it is also to the specialist in insurance medicine.

"The instrument consists of a rigid reservoir of very light metal into which is set an air-tight collapsible chamber, also of metal, which expands and contracts with the pressure communicated to it from the rubber cuff encircling the arm. Attached to the upper member of this chamber is a bell crank assembly which gives a circular motion to the chart disk as the pressure in the reservoir decreases. The chart disk carries a circular chart which receives the curves written by a pen in response to the pulsations of the artery. Thus no clock or motor is used to drive the kymograph, and as the calibrations are printed on the chart the position of certain definite points in the curve gives the reading in millimeters of mercury directly from the chart.

"The curve is traced by a pen actuated by a small diaphragm receiving its impulses directly from an independent cuff on the arm. The oscillations are written as a series of spikes, the first one of which indicates the systolic pressure and a certain point occurring later in the tracing gives the diastolic reading. The pulse pressure is calculated in the usual way.

"The application of the instrument does not differ materially from the ordinary sphygmomanometer. The cloth sleeve containing the separate rubber cuffs is placed on the arm above the elbow, care being used to assure the placing of the upper or

filter cuff proximal to the lower or recording cuff, which should have its lower margin just above the bend of the elbow. Each cuff has its own circuit through the instrument. The upper cuff communicates with the tank or reservoir and also with the oscillometer in a way to prevent the first waves from

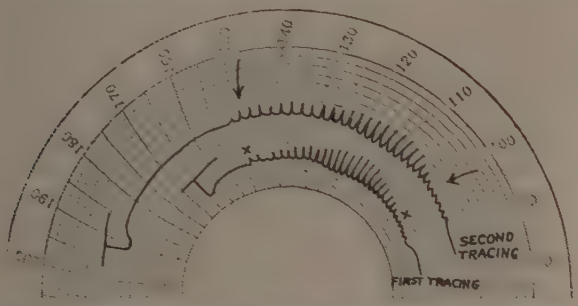

FIGURE 1. — Characteristic curve: second tracing, systolic 147, diastolic 95; first tracing, systolic 147, diastolic 94. (Courtesy of Amer. Med. Assn.)

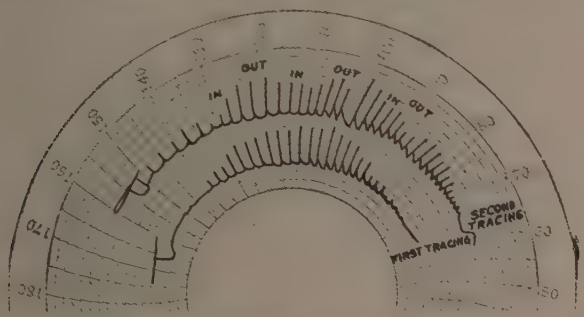

FIGURE 2. — Curve showing influence of respiration and other factors: first tracing normal respiration, systolic 137, diastolic 85; second tracing forced respiration showing rise and fall of spikes; a gap is noticed just below 100; rate somewhat irregular. (Courtesy of Amer. Med. Assn.)

impinging on the upper border of the recording cuff and obscuring the criterion of systolic pressure. The lower cuff is connected directly to the oscillometer diaphragm and to a minimal value in such a way that it transmits to the pen the volume changes of the artery occasioned by the pulse.

"After the sleeve has been adjusted to the arm, the pneumatic cuffs are inflated with air by means of a small bulb until the circulation in the arm is entirely cut off. This can be determined by placing the bell of a stethoscope over the artery

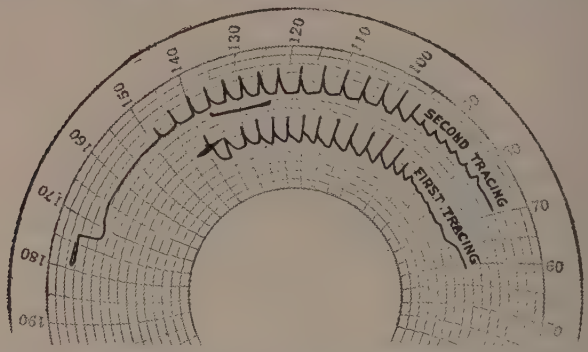

FIGURE 3. — Curve showing sinus arrhythmia: increase in rate from 125 to 135; second tracing, systolic 148, diastolic 92; first tracing, inflation was not carried high enough to obliterate artery. (Courtesy of Amer. Med. Assn.)

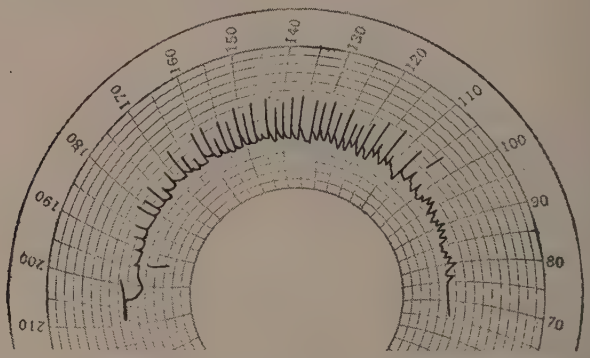

FIGURE 4. — Curve showing auricular fibrillation: systolic 165, diastolic probably 102; in any case, much more accurate than auscultatory method; other factors in this patient affect this curve also. (Courtesy of Amer. Med. Assn.)

just below the sleeve and observing the point at which the sounds cease, or inflation may simply be carried to a pressure which experience would teach us was in excess of the arterial tension of a given patient. Should the pressure not be sufficient

to obliterate the lumen of the artery, it is only necessary to trace an extra curve when it can be carried higher.

"After the system has been inflated sufficiently, a valve is opened and deflation begun. As soon as air flows through the leak, the chart begins to revolve at a rate dependent on the size of the leak. The pen traces a smooth line (if the circulation has been entirely cut off) for some distance; then at the point where the blood passes under the filter cuff a noticeable spike is seen to rise above the line, pointing toward the periphery of the chart. This represents the systolic pressure and will coincide exactly with the first sound heard on auscultation. The rotation of the chart is so synchronized with the decrease in pressure in the filter cuff that the point on the chart, as shown by the marginal calibration, will be the precise measure of systolic blood pressure. This may be verified easily with the stethoscope. It should be remembered, however, that typical sounds are not always present in every artery. This is one of the points of superiority of the graphic method.

"Further deflation will give a series of spikes and a progressive widening of the space at the bottom of the wave, a notch supported on the descending limb and an increase in the height of the spike. As the zone of diastolic pressure is reached there is a distinct drop in the wave, and the spikes become progressively shorter, more or less abruptly, depending on the elasticity of the vessel coats. At the point where the rapidly descending tops of the spikes become of more nearly equal length will be found the index of diastolic pressure. This coincides very accurately with the beginning of the fourth phase in the sound sequence. Depending somewhat on the rate, the first or second spike below the point described above will in some cases be a more precise reading. The difference is, however, only 1 or 2 mm.

"The criterion originally adopted by Korotkow was the total disappearance of sound, and directions for identifying this point in the curve will appear later. This criterion is not recommended, however.

"The anesthetist and the psychologist will be interested in the ability of the instrument to trace serial curves. Nine or ten of these may be written on the same chart. To accomplish this the first curve is written very near the center of the chart and, when finished, the cuffs are reinflated and a second tracing made a few millimeters nearer the periphery by turning the adjusting screw on the pen arm assembly through a small arc, thus causing the pen to write in a new path. By connecting the systolic points together with a line, the changes in the magnitude of the pressure can be easily represented. The same may be done with the diastolic readings. It should be noted that successive systolic pressures are usually lower and the diastolic pressures higher, as a result in the first case of the lessening psychic influence and in the latter of the stasis in the arm distal to the constriction.

"As the instrument must be used on patients with widely differing pulse rates, the travel on the chart must be controlled so that the proper configuration can be given to each wave on any subject. After much experiment it has been found that the most consistent readings are secured by distorting the wave until it resembles a spike. A dial is provided on each instrument indicating the amount of leak necessary to produce this character in the wave. Before a tracing is made, the dial is simply turned to a figure corresponding to the pulse rate of the patient.

"While the instrument is not intended to be used as a pulse wave recorder, many of the classic irregularities are character-

istically shown. Our greatest interest in them, however, lies in their possible influence on the critical points of the curve with relation to pressure.

"An inspection of the accompanying tracings (Figs. 1 to 4) will illustrate the several points mentioned. It would seem that in very few cases will any arrhythmia materially affect the reading of the pressure."

Bibliography

1. Stocks, P. and Karn, M. N.: Blood Pressure in Early Life. Cambridge University Press, London, 1924.
2. Korotkoff, N. S.: Zur Methodik der Blutdruckmessung. Mitt. d. k. mil. med. Akad. zu St. Petersburg. **2**: 365, 1905.
3. Gibson, P. C.: Silent gap in auscultatory estimations of blood pressure, Lancet **2**: 1012, 1927.
4. Mudd, S. G. and White, P. D.: The auscultatory gap in sphygmomanometry, Arch. Int. Med., **41**: 249, 1928.
5. Warfield, L. M.: Studies in auscultatory blood pressure phenomena. Arch. Int. Med., **10**: 258, 1912.
6. Barr, Daniel R.: A new recording sphygmomanometer, Jour. Am. Med. Assoc., **89**: 1513, 1927.

CHAPTER IV

CAPILLARY AND VENOUS PRESSURE. HYPOTENSION

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THE CAPILLARY BLOOD PRESSURE

Ernst P. Boas

Some knowledge of the capillary blood pressure and of its variations in health and disease is of considerable importance to an understanding of the physiology of the circulation, of the mechanism of edema and of a number of clinical syndromes. The capillary blood pressure represents the head of pressure of the blood in the capillaries. It is composed of two elements, the pressure generated by the heart beat and transmitted through the arterial tree, and the hydrostatic pressure, determined by the weight of the column of blood between the level of the heart and the particular part of the body that is being studied. The blood pressure in the arteries undergoes a gradual reduction, starting from the aorta and approaching the periphery. In the radial artery it is about ten millimeters of mercury

lower than in the aorta, and in the digital arteries it has dropped approximately another ten millimeters. The chief drop, however, occurs in the arterioles before the capillaries are reached, for the capillary blood pressure ranges between 10 and 25 millimeters of mercury.

The capillary pressure must not be regarded as fixed and unchanging; it is in a constant state of flux. Since it is determined chiefly by the head of pressure transmitted through the arterial tree, it will fluctuate depending on the degree of contraction of the arterioles. Arteriolar dilatation will determine a higher capillary pressure, arteriolar constriction a lower one. Similarly a very marked interference with venous outflow may cause a backing up of blood and an elevation of capillary pressure. Because of its primary dependence on the pressure in the arterioles and on their degree of dilatation, the capillary blood pressure in different capillaries will not be the same always, for within one small area the tone of the different arterioles may vary.

In addition to these fluctuations caused by changes in the caliber of the arterioles, the capillaries themselves undergo independent contraction and dilatation. This too must be of influence on the pressure of the blood within them. In spite of the close relations between arteriolar pressure and capillary pressure, the capillary pressure and the arterial blood pressure, as measured by the ordinary clinical instruments, do not vary in the same direction, and the capillary pressure shows considerable independence from that in the large arteries.

As Starling[1] pointed out twenty years ago, the capillary blood pressure is the filtration pressure which directs, so to speak, the passage of water from the blood to the tissues. It is counteracted by the colloid osmotic pressure of the blood, which

tends to retain water within the vessels. A normal water exchange is dependent on a proper balance between the pressure of the blood in the capillaries and the colloid osmotic pressure of the blood. A rise in capillary pressure with an unchanged osmotic pressure, or a fall in colloid osmotic pressure with an unchanged capillary pressure will determine a loss of fluid from the blood to the tissues which, if of sufficient extent, will cause edema. Of course, the mechanism is not so simple as this would make it appear, and many other factors are involved such as, for instance, capillary permeability. One illustration, however, may demonstrate the significance of this relationship. If a person stands quietly for a long time with the hands hanging at the side, plethysmographic measurements will show a considerable swelling of both hands and feet. This is due to the effect of the hydrostatic pressure of the column of blood between the heart and the dependent part, which superadded to the capillary pressure overcomes the colloid osmotic pressure and allows fluid to escape from the blood to the tissues. A more detailed consideration of this whole problem may be found in Krogh's[2] lectures.

Methods of Estimating Capillary Pressure

The first to measure capillary pressure was von Kries[3], who determined the pressure necessary to produce blanching of the skin. A number of modifications of his method were introduced which are now only of historic interest. Following Lombard's[4] discovery of a method of visualizing the capillaries by placing a drop of oil on the skin and studying them directly under a microscope, various modifications of his pressure chamber, by means of which the capillaries could be compressed while being visualized under the microscope, have been introduced. The most valuable of these are by Danzer and Hooker[5], Kylin[6], Vigevani[7] and Luisada[8].

I have worked a good deal with the Danzer and Hooker apparatus and have found it very satisfactory. The pressure of the capillaries of the skin, for these are the only ones accessible to measurement in man, as determined by this instrument, is from 20 to 25 millimeters of mercury. Kylin reports figures from 10 to 15 millimeters of mercury, and Luisada's are considerably higher. Leonard Hill[9] and Rajka[10], each employing totally different methods, obtain much lower values, about 2 millimeters of mercury. Finally, Carrier and Rehberg[11], by inserting a very fine glass capillary tube into the capillaries, obtained values of from 4 to 6 millimeters of mercury. When these latter figures are corrected for the hydrostatic difference when the hand is held at heart level, as in Danzer and Hooker's method, they read about 15 millimeters of mercury. For clinical and comparative purposes the method of Danzer and Hooker will be found to give adequate results. The probable accuracy of the figures obtained by this method is supported by the figure for the colloid osmotic pressure of the blood, which is from 21 to 27 millimeters of mercury, and which, as our earlier considerations have shown, must balance the capillary blood pressure.

Capillary Pressure in Health and Disease

Cold lowers and heat raises capillary blood pressure. Posture, too, is of influence. The capillary pressure is lowest in the recumbent, higher in the sitting and highest in the standing posture. The diurnal variation is slight. Increased intrathoracic pressure raises, and diminished intrathoracic pressure lowers the capillary blood pressure.

The study of the capillary pressure in patients with hypertension has been of the greatest interest. Kylin reported high capillary pressures in patients with glomerulonephritis and

hypertension, and normal figures in patients with essential hypertension. He further studied 20 scarlet fever convalescents daily and found in some a marked increase in capillary pressure. In 3 of these patients a typical glomerulonephritis with albumin, casts and red blood cells in the urine developed several days after the capillary pressure had risen. The highest pressure observed ranged from 40 to 55 millimeters of mercury. He concludes that there are two types of hypertension, essential hypertension (an arterial hypertension), and glomerulonephritic hypertension (a capillary hypertension). The hypertension is not the result of the kidney disease, but the glomerulonephritis is a manifestation of a diffuse capillary injury caused by toxins of certain acute infectious diseases.

Unfortunately Kylin's observations have not been generally confirmed. Gobel[12] observed a number of patients with glomerulonephritis and normal capillary pressures. With Frant[13] and Mufson[14] I studied 45 patients with hypertension, and found 17 with high capillary pressures and 28 with normal or low pressures. The high pressures varied from 30 to 90 millimeters of mercury. The patients with high and low capillary pressures could not be distinguished clinically. Most were suffering from essential hypertension. Necropsy studies of four patients with high capillary pressures revealed no trace of glomerulonephritis; indeed, in one case the kidneys were essentially normal. We studied several patients with acute glomerulonephritis who had normal capillary pressures. The significance of high capillary pressures in patients with hypertension is still obscure. Yet a high capillary pressure has some prognostic value. In a period of 15 months, 8 of 17 patients with high capillary pressures, and only 5 of 28 with low capillary pressures, died.

High capillary pressures have been observed in the nephritis

of pregnancy and in eclampsia[15, 16, 17]. Mufson has found that in the hypertensive toxemias of pregnancy a low capillary pressure showed a favorable maternal and fetal prognosis, while a high capillary pressure often was of serious import to mother and child.

It is probable that in some cases at least, capillary disease or constriction precedes and may determine a rise in blood pressure. Bechmann[13] has offered some experimental support to this view.

In acrocyanosis the capillary pressure in the capillaries of the hands is low[19]. When the hands are placed in hot water, the capillary pressure rises. This points to arteriolar constriction as the prime cause for this vasomotor disturbance.

In patients with cardiac insufficiency, even when the venous pressure is elevated, the capillary pressure is normal or low[20]. This observation is of considerable theoretic interest. It affords evidence of the functional independence of the capillaries. It gives additional support to the view, so stoutly defended by the late Sir James Mackenzie, that peripheral stasis is conditioned not by back pressure effects, but rather by a lessened propelling force of the left ventricle. This diminished motive power of the heart results in a slowing of the blood stream, particularly in the peripheral vessels. The capillaries become dilated, possibly due to oxygen lack, and their walls become more permeable and so favor the formation of a filtration edema.

Venous Pressure

Venous pressure in man was first studied by Hooker and Eyster[21]; in this publication a method was described for the determination of venous pressure which was later somewhat modified to a more convenient procedure by N. W. Brown[22].

Venous pressure is measured in centimeters of water; the normal values lie between 8 and 20 cm., though in old age it rises and may be 26 cm. or higher in persons over 70 years. Eyster and Middleton[23] concluded that the normal venous pressure never exceeds 11 cm. in the recumbent position. Clark[24] demonstrated a diurnal variation, finding the venous pressure to be lower during sleep; with cardiac decompensation, on the other hand, the higher pressure occurs at night. This may be one of the factors responsible for the nocturnal dyspnea so often seen in patients with an insufficient myocardium. This diurnal variation is about 9 cm. in normal and 12 cm. in cardiac cases. Hard exercise increases venous pressure.

A rise of venous pressure may be a sign of obstruction in a given vein as in Brown's[22] patient with a thrombosis of the left subclavian vein, whose left hand showed a venous pressure of 30 cm., while that on the right was only 16. The main value of venous pressure readings is the measure they furnish of the efficiency of the right ventricle. When the right ventricle, for any cause whatsoever, allows residual blood to accumulate within it, the venous pressure will rise. As Eyster and Middleton[25] have indicated, a measure primarily of right heart efficiency exists in the venous pressure determination; ultimately this becomes a measurement of myocardial competency in general. Clark[24] showed that a venous pressure above 20 cm. of water was a sign of cardiac failure, and this seems to have been accepted generally; in his studies he found that a reading as high as 50 cm. could occur. Among Clark's[24] observations there were several that had a very distinct clinical bearing; these were, that, urine volume and venous pressure vary inversely and, that, thoracentesis in myocardial insufficiency lowers the venous pressure.

There is at least one exception to Clark's[24] interpretation of a venous pressure of 20 cm. of water or higher as being absolutely indicative of cardiac decompensation. This, according to Blumgart and Weiss[26], is found in cases of arterial hypertension; one of their patients, without any signs of heart weakness, showed a venous pressure of 25 cm.; these authors mention that H. J. Sewall and others have published this fact previously. This, however, is not true for all hypertensives, as a normal venous pressure is the rule rather than the exception (Clark, Brown).

Eyster and Middleton[25] have considered a venous pressure of 20 cm. of water, which was ascending, as an indication for venesection in cases of myocardial insufficiency. They withdrew 500 c.c. of blood, since Meek and Eyster[27] have demonstrated that the removal of approximately such an amount is necessary to effect a decrease in the size of the heart. As a result of their investigations Eyster and Middleton[15] come to important conclusions regarding venous pressure in relation to venesection: "If the heart muscle responds adequately to the reduced load, the venous pressure will remain low, and the subjective and objective evidences of cardiac decompensation will subside. On the other hand, an early sharp rise in the venous pressure, or a steady return to its original high level, points to a lack of myocardial reserve and no continued clinical improvement can be expected." This is a little more hopeful than Clark's earlier experience that venesection never lowered venous pressure for more than a very brief period. It would seem that the determination of venous pressure in the management of cases of cardiac decompensation has been neglected, and that it could be employed very well to advantage as a routine clinical procedure.

Hypotension

Two recent monographs, published in book form, "Hypotension" by Alfred Friedlander[28] and "Low Blood Pressure" by J. F. Halls Dally[29], contain a detailed discussion of this subject.

It is difficult to state exactly what level marks the border line between normal and low blood pressure. From a study of the normal tables in Chapter II some idea of what constitutes a low blood pressure may be derived. A systolic pressure of 110 mm. or less has been accepted generally as indicative of hypotension in adults; the corresponding diastolic values, according to Dally[29], are 66 mm. of mercury for men and 62 mm. for women.

There are two points of view that may be held regarding a blood pressure below the average normal; either it must be regarded invariably as a symptom (all authors apparently agree that it is a symptom and not a primary manifestation) of some constitutional or acquired bodily disturbance, or it may, at times at least, be the expression of normal health.

Barach[30] shows that the incidence of low blood pressure in apparently healthy persons is about 3.5 per cent., and that this is a fairly constant finding. Friedlander[28], after a statistical study of the situation, gives a somewhat lower figure of 2 to 3 per cent. In any event, the number of hypotensive individuals is considerable, and consequently the subject deserves thought and consideration.

It is freely acknowledged by most physicians that persons with a low blood pressure may be normal in every way, that in strength, endurance, mentality, etc., they may equal or even exceed the average. The occasional statements that a blood pressure of 90 mm. or less dooms the individual to a permanently

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languid and ineffectual existence do not, I believe, agree with the facts. Dally[29] says emphatically that; "Low arterial pressure, whether congenital or acquired, temporary or permanent, is always to be regarded as an expression of low vitality", and his explanation of the display of strength and achievement of a hypotensive is that this is only a flash in the pan, a temporary affair, to be followed by signs of exhaustion, when the effort has been a prolonged one. It is only rational to consider the existence of a hypotension in much the same light as that of blood pressure in general, as attempted in Chapter I. The blood pressure value expresses the potential energy which can be utilized to produce a circulatory flow through the arterioles to the capillaries. The degree of constriction of the arterioles controls the amount of blood that enters the corresponding capillary area. When the heart action is vigorous and the arterial tone is high, the blood flow would accelerate, were it not for the peripheral control, the stop-cock action, of the arterioles; under these circumstances the blood pressure would rise. However, the nutritional function of the blood, carried out in the capillaries, is just as efficient with a lower level of arterial pressure as with a higher one, since the arterioles control the capillary supply, keeping it constant, regardless of the height of the blood pressure. Because of this compensatory regulation by the arterioles no evidence of circulatory embarrassment manifests itself when arterial pressure assumes a lower level for one or two weeks before death in chronic diseases (see Table 4). In these cases the muscles of the heart and the larger arteries finally become so weak that they cannot maintain an adequate circulation and death follows. The main point, in the present consideration, is that these individuals give no evidence of circulatory insufficiency, though their blood pressure is much lower for some days before they die than previously.

The above considerations make it possible to assume that there are individuals whose circulation is so adjusted that their blood pressure is maintained at a lower level than normal, and yet that through the compensatory action of the arterioles there is no reduction in the quantity of blood brought to the capillaries and, therefore, no diminution of circulatory efficiency in spite of the hypotension. This suggests the mechanical problems coming up every day in regard to coal or oil or gas consumption by engines required to deliver a certain amount of service. Two engines apparently very much alike may differ enormously in this respect, and yet both be satisfactory except in maintenance cost. To strive to raise a low blood pressure in a person who seems in normal health and vigor, to consider such an individual diseased, is a mistake, especially, since life insurance statistics have shown that low blood pressure cases have a longer life expectancy than their contemporaries with a normal, let alone a high blood pressure. Dally's[29] belief that low blood pressure cases necessarily suffer with periods of depression after even moderate physical or mental strain, thus putting these patients in a low vitality group, is not accepted universally. Janeway[31] says, "I have personally observed systolic pressures which would ordinarily be considered subnormal, below 110 in men and 95 or 100 in women, existing over long periods of absolutely perfect health and physical activity".

One of the best proofs indicating that height of blood pressure is adapted to the individual is that the level of blood pressure in the Oriental peoples is so low as to constitute a hypotension, according to European and North American standards. This is a wholesale example of low blood pressure in accord with normal strength and endurance. This difference cannot be attributed directly to the climate as the white races maintain the

Conditions Commonly Associated with Hypotension	Cause for the Hypotension
Anaphylactic shock	Dilatation and congestion of large venous trunks of splanchnic area, coincident with medullary anemia.
Traumatic shock	Toxic factor (histamin?) increasing permeability of capillary walls and a consequent reduction of blood volume by escape of plasma into the tissues.
Surgical shock	Several factors concerned: Loss of blood from hemorrhage Tissue trauma liberating toxic material Prolonged anesthesia produces dilatation of peripheral vessels General or spinal anesthesia lowers blood pressure Visceral trauma produces dilatation of splanchnic arterioles, capillaries and venules.
Infectious diseases	Blood flow in capillaries slower than in health
typhoid fever	Increased body temperature
pneumonia influenza	Weakened heart action due to degeneration of heart muscle
typhus fever malaria	Loss of splanchnic tone due to toxemia and in part to weakened arterial musculature
trichinosis	Cachexia
pulmonary tuberculosis	Loss of blood volume due to toxic action on capillaries, diarrhea, hemorrhage, etc.
Amyloid disease	Cachexia, amyloid infiltration surrounding and in the walls of smallest arteries, capillaries and veins.
Addison's disease	Tuberculosis of the adrenal glands Cachexia, diarrhea.
Secondary anemia Pernicious anemia Status lymphaticus Infantilism Myasthenia gravis Adiposis dolorosa	Diminished viscosity of the blood? Weakness of all muscular tissues.

TABLE 17. — Some of the more common clinical conditions associated with hypotension and the reasons ascribed for the low blood pressure. The table is largely summarized from the monograph of Alfred Friedlander.

blood pressure level peculiar to them when in the Orient and vice versa. If a low blood pressure is to be regarded as normal for some peoples, it is only to be expected that at least some members of the white race should have constitutional characteristics approaching theirs. Cadbury[32] and others have shown that in the Chinese the average blood pressure is 20 to 30 mm. less than our accepted standards. In 60 per cent. of Cadbury's observations the blood pressure was 110 mm. or less. In India, the Hindus show a systolic blood pressure of about 100 mm. of mercury. The Filipinos also have a low blood pressure.

Some of the principal conditions associated with hypotension are summarized with the causes for the low blood pressure in Table 17. These data have been largely obtained from Friedlander's monograph. The treatment of these individual forms of hypotension is naturally suggested by the cause in each instance.

Essential Hypotension

There is a clinical syndrome which has received this name. A low blood pressure is a part of this symptom complex, and because attention has been focused so largely on this feature, it has been called essential hypotension in spite of the fact that we do not know whether the characteristic arterial pressure is a symptom or a cause of the malady. In the preceding section it has been pointed out that a person may be normal in every way and yet have a blood pressure below the average. There are some individuals who are lethargic, have no endurance and suffer from cardiac palpitation after moderate exertion; they are easily depressed and not capable of mental effort; their hands and feet are cold, moist and cyanotic; they complain of headache, pains in the chest, limbs and elsewhere; their appetite is capricious, and they suffer from various "dyspeptic" symp-

toms; they sleep poorly; this is the composite symptomatology derived from many sources. The main point appears to be that these patients complain of more or less constant physical and mental exhaustion and not of any focal symptoms. Friedlander[29] stresses the fact that they are not to be regarded as neurasthenic, psychasthenic, or psychoneurotic subjects.

Physical examination reveals no organic lesions, but there are the changes generally regarded as characteristic of low vitality: nutrition is not good, corresponding to the poor appetite; the eyes are a little sunken and the folds beneath them are unnaturally deep and pigmented; the heart is of the "drop type", with somewhat feeble sounds; the chest and abdomen are narrow and long, conforming to the "visceroptotic habitus"; the blood pressure is low and the pulse is prone to be rapid; the hands and feet are cold, moist and cyanotic. In short, these patients in their build, the quality of their tissues and their functions show a typical picture of a lowered vitality. This description might apply very well to the cases of neurocirculatory asthenia brought to the fore among the recruits during the World War, a large group that passed medical inspections successfully, but were unsatisfactory in physical strength and endurance.

The cause for essential hypotension has been sought in various directions; Barach[30] ascribes it to a poor respiratory apparatus and consequent inefficient oxygenation; Fossier[33] believes it to be the result of splanchnoptosis; this may possibly carry with it the idea of the accumulation of an excess quantity of blood in the splanchnic area, so often mentioned as of etiological significance; Friedlander[28] advances the "theory of capillary stasis" brought on by the accumulation of small quantities of histamin or histamin-like bodies, which bring

about a dilatation of the capillaries and "pooling of the blood within them" and favor an escape of plasma into the surrounding tissues, thus diminishing the blood volume; focal infections are mentioned by Hoxie[34]; many believe that essential hypotension is an expression of low vitality. Dally[29] concurs in this opinion, and he would ascribe such an etiology to all types of hypotension. The syndrome as a whole may be looked upon as due to a lowered vitality; inasmuch as the clinical picture is a permanent one there must be some constitutional cause for it, bodily build, metabolic anomaly, or endocrine disturbance. Of these the first is known to be a factor, the other two are conjectural only.

The advisability of considering hypotension as a clinical entity is very doubtful. It may be argued that because essential hypertension is so designated, the same place in clinical medicine should be accorded to low blood pressure. The reason for this difference is that, while a persistent hypertension is a condition entailing dangerous and often fatal results, hypotension in itself is harmless and, as a symptom, should not receive treatment. Furthermore, we are absolutely ignorant of the causes of essential hypertension, while those for the constitutional low blood pressure at least have been approached.

Treatment of Essential Hypotension

That the treatment of this condition is difficult may be gathered from the discouraging results obtained in attempting to fashion "front-line troops" from the "neuro-cardiac asthenic" group of recruits. In one case of essential hypotension a cure of the subjective symptoms was effected, after much study, by following the formula of two weeks' vacation in the open every two months. This, in reality, is no cure at all but only a way

of adjusting the individual to his own physiological powers, which would seem the best method of treating such cases.

Habits of work, of rest, sleep, intestines and daily routine must be adapted to the needs of each patient; the diet should be nutritious and so regulated that full normal weight is maintained; a sufficient amount of fluid must be insisted on since a tendency to constipation, excessive concentration of the blood, a dry mouth and skin are induced by neglect to take about one and one half quarts of liquid a day; alcohol is permissible and often beneficial; massage, hydro- and electro-therapy all have their usefulness; sunlight, natural if possible, otherwise artificial, should be advised; a daily forty-minute walk taken in the sun is one of the most desirable elements in the treatment; the most valuable of all is that of outdoor vacations taken at frequent intervals and away from the dictates of fashion and civilization, such as camping, hunting or fishing trips.

When the etiology of this condition is scanned, two specific forms of therapy suggest themselves. These are the removal of infectious foci and the strengthening of abdominal muscles, with the wearing of an abdominal support, while attempts are made to increase the abdominal fat. Drugs have not been much advocated; atropine is recommended by Lawrence[35]; caffeine, strychnine, ergot, ephedrine and the internal secretions all have been used, but it may be well to adapt them to the special indications in each case and not to resort to them as a routine measure.

Bibliography

1. Starling, E. H.: Fluid of the Body, London, 1909.
2. Krogh, A.: Anatomy and Physiology of the Capillaries, Yale Univ. Press, 1922.

3. v. Kries, N.: Ber. d. sächs. Ges. d. wiss. mathem.-physik. Kl., **27**: 148, 1875.
4. Lombard, W. P.: The blood pressure in the arterioles, capillaries and small veins of the skin, Am. Jour. Physiol., **29**: 335, 1912.
5. Danzer, C. S. and Hooker, D. R.: Determination of the capillary blood pressure in man with the microcapillary tonometer, Am. Jour. Physiol., **52**: 136, 1920.
6. Kylin, E.: Studien über das Verhalten des Kapillardrucks, Zentralbl. f. inn. Med., **41**: 505, 1920: Clinical Determination of Capillary Tension, Acta Med. Scandinav., **57**: 566, 1923.
7. Vigevani, G.: L'osservazione diretta e la pressione sanguigna dei capillari in rapporto alla clinica, Arch. di Patol. e. clin. Med., **2**: 284, 1923.
8. Luisada, A.: Un nouveau tonometre capillaire, Press Med., **33**: 1725, 1925.
9. Hill, L. and McQueen, J. M.: The measurement of capillary blood pressure in man, Brit. Jour. Exp. Path., **2**: 1, 1921.
10. Rajka, E. and Wessely, E.: Ueber das Verhalten des Kapillardruckes unter physiologischen und pathologischen Verhältnissen, gemessen mit dem Török-Rajka-Wesselyschen Kapillartonometer, Ztschr. f. d. ges. exper. Med., **57**: 171, 1927.
11. Carrier, E. B. and Rehberg, P. B.: Capillary and venous pressure in man, Skand. Arch. Physiol., **44**: 20, 1923.
12. Gobel, I.: Ueber Schwankungen im Kapillardruck, Klin. Wchnschr., **2**: 2279, 1923.
13. Boas, E. P. and Frant, S.: The capillary blood pressure in arterial hypertension, Arch. Int. Med., **30**: 40, 1922.
14. Boas, E. P. and Mufson, I.: The capillary blood pressure in arterial hypertension and in nephritis, Jour. Lab. and Clin. Med., **9**: 152, 1923.
15. Grzechowiak, F.: Der Kapillardruck besonders während d. Schwangerschaft, Ztschr. f. Geburtshilfe u. Gynäk., **87**: 129, 1924.
16. Nevermann, H.: Kapillardruckmessungen, Klin. Wchnschr., **3**: 1433, 1924.
17. Mufson, I.: The capillary pressure in the toxemias of pregnancy, Am. Jour. Obst. and Gynec., **15**: 800, 1928.
18. Beckmann, K.: Ueber die Beziehungen zwischen Blutdruck, Kapillardruck u. Nierenveränderungen im Tierexperiment, Deutsch. Arch. f. klin. Med., **149**: 177, 1925.
19. Boas, E. P.: The capillaries of the extremities in acrocyanosis, Jour. Am. Med. Assoc., **79**: 1404, 1922.

20. Boas, E. P. and Dooneief, G.: The mechanism of peripheral stasis in myocardial insufficiency, Arch. Int. Med., **33**: 407, 1924.
21. Hooker, D. R. and Eyster, J. A. E.: An instrument for the determination of venous pressure in man, Bull. Johns Hopkins Hosp., **19**: 274, 1909.
22. Brown, N. W.: A simple method for the determination of venous pressure, Bull. Johns Hopkins Hosp., **29**: 93, 1918.
23. Eyster, J. A. E. and Middleton, W. S.: Clinical studies on venous pressure, Arch. Int. Med., **34**: 228, 1924.
24. Clark, A. H.: A study of the diagnostic and prognostic significance of venous pressure in cardiac diseases, Arch. Int. Med., **16**: 587, 1915.
25. Eyster, J. A. E. and Middleton, W. S.: Venous pressure as a guide to venesection in congestive heart failure, Am. Jour. Med. Sc., **174**: 486, 1927.
26. Blumgart, H. L. and Weiss, S.: Clinical studies on the velocity of blood flow, Jour. Clin. Invest., **5**: 343, 1928.
27. Meek, W. J. and Eyster, J. A. E.: Reactions to haemhorrhage, Am. Jour. Physiol., **56**: 1, May, 1921.
28. Friedlander, A.: Hypotension, The Williams & Wilkins Co., Baltimore, 1927.
29. Dally, J. F. Halls: Low Blood Pressure, London, 1928.
30. Barach, J. H.: Arterial hypotension, Arch. Int. Med., **35**: 151, 1925.
31. Janeway, T. C.: Important contributions to clinical medicine during the past 30 years from the study of human blood pressure, Bull. Johns Hopkins Hospital, **26**: 341, 1915.
32. Cadbury, Wm. W.: Blood pressure of normal Cantonese students, Arch. Int. Med., **30**: 362, Sept., 1922.
33. Fossier, A. E.: A cause of essential hypotension, Am. Jour. Med Sc., **171**: 496, 1926.
34. Hoxie, G. H.: Endocrine therapy in cases of low blood pressure, Endocrinology, **5**: 773, 1921.
35. Lawrence, C. H., Jr.: Some aspects of hypotension, Interstate Med. Jour. **23**: 165, 1916.

CHAPTER V

TESTS FOR FUNCTIONAL EFFICIENCY OF THE CIRCULATION

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The Blood Ptosis Test, The Crampton Index

C. Ward Crampton

The blood ptosis test is based upon the difference of the systolic blood pressures and heart rates in the standing position and the recumbent position. It was reported in 1903[1], published in 1905[2]. It has been followed by various tests of similar nature by Foster[3], McCurdy[4], Meylan[5] and Schneider[6].

The basic record is the systolic pressure and the heart rate in the recumbent position. These are compared with the same records taken standing. The patient, when standing, imposes a hydrostatic load upon the circulation. This load is constant to the individual. It calls into action the gravity-resisting mechanism of the body.

The action of the circulation under the load differs in different individuals and varies in the same individual depending largely upon the state of efficiency of the gravity-resisting ability of the circulation. The systolic pressure may be higher in the standing position, indicating an efficiency of the mechanism or an over-efficiency of the same. A rise of 5 to 10 millimeters is common.

If the pressure falls on standing, it indicates a deficiency. A fall of 10 to 30 millimeters is common. Cases showing a fall of 80, 84, 100, 106, 110 millimeters are on record and probably will be noted more frequently as the method is applied more widely to the sick.

The second circulatory reaction to the hydrostatic load imposed on the circulation on standing is a change of heart rate. It is almost invariably more rapid in the vertical position. It commonly increases 8 to 10 beats a minute, uncommonly from 40 to 65 beats a minute. This increase is due to a stimulation of the acceleration mechanism in an endeavor to compensate for a falling blood pressure. No increase is found in the condition of extraordinary bodily vigor. An increase is common in ordinary health and marked in asthenias.

There are, therefore, two signs of efficiency, the raised systolic pressure and the unchanged heart rate. Correspondingly, there are two signs of relative inefficiency, lowered systolic pressure and a decided increase in the rapidity of the heart.

Without forcing the conclusion that changes in heart rate and blood pressure are the same physiological reactions, one may, for the sake of convenience of record and statistical handling, establish an index which includes plans of these two factors. This index is useful, but not essential. From 2,000 records of apparently healthy young men, it was established that the range

of systolic pressure was commonly from a rise of 10 to a fall of 10 millimeters and that the range of heart rate increase was

Heart-rate Increase	Blood Pressure Increase										Blood Pressure Fall									
	20 to 19	18 to 17	16 to 15	14 to 13	12 to 11	10 to 9	8 to 7	6 to 5	4 to 3	2 to 1	0	− 1 to − 2	− 3 to − 4	− 5 to − 6	− 7 to − 8	− 9 to − 10	− 11 to − 12	− 13 to − 14	− 15 to − 16	− 17 to − 18	− 19 to − 20
0 to 4	125	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25
5 to 8	120	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20
9 to 12	115	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15
13 to 16	110	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10
17 to 20	105	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5
21 to 24	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0
25 to 28	95	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5
29 to 32	90	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10
33 to 36	85	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10	− 15
37 to 40	80	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10	− 15	− 20
41 to 44	75	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10	− 15	− 20	− 25
45 to 48	70	65	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10	− 15	− 20	− 25	− 30
49 to 52	65	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10	− 15	− 20	− 25	− 30	− 35
53 to 56	60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10	− 15	− 20	− 25	− 30	− 35	− 40
57 to 60	55	50	45	40	35	30	25	20	15	10	5	0	− 5	− 10	− 15	− 20	− 25	− 30	− 35	− 40	− 45

TABLE 18. — Scale of gravity resistance value (blood ptosis, Crampton index).

EXAMPLES

CASE 1. Athlete in good condition.

	Pulse Rate	*Systolic Pressure*	
Horiz.	64	120	
Vert.	64	130	
	0	+ 10	Index 100

CASE 2. Same. Apparently in good condition. Sick, tonsilitis for the next two weeks.

Horiz.	74	122	
Vert.	96	110	
	+ 18	− 12	Index 25

CASE 3. Woman, aged 45, Tuberculosis

Horiz.	90	108	
Vert.	110	82	
	+ 20	− 26	Index Minus 10

CASE 4. Woman, aged 50, Diabetes

Horiz.	80	178	
Vert.	96	88	
	+ 16	− 90	Index Minus 165

from 0 to 44. With a fair assumption that these ranges were of similar value, they were matched on the scale shown in Table 18.

Conduct of the Test

The patient stands. The blood pressure instrument is adjusted to the arm. The pulse rate is counted by 5-second periods until an even rate is noted and recorded. The usual blood pressure records are made. The patient reclines and is made comfortable. The pulse rate is watched until it no longer falls and is recorded. The pressures are then taken. The diastolic pressures are noted of course. They are less mobile than the systolic pressures and carry their own significance outside the immediate field of the test. It should be remembered that the test shows the efficiency of the gravity-resisting ability of the circulation at the time it is taken. This varies rapidly under many influences.

Physiological Basis

The veins of the abdomen are capacious enough to accommodate the total blood volume. In the terminal vasomotor paralysis of infectious fevers, death occurs from accumulation of blood in the splanchnic area. As the tone weakens less and less blood gets to the heart, which discharges its lessening quota with increasing rapidity. It suffers in common with the rest of the body from lack of blood, becomes irregular and stops. Vasotone failure commonly precedes heart failure. Splanchnic vasotone is essential to life. Good vasotone supports all life processes. Poor vasotone lets them down. Conversely, impairments, fatigue and illness (with conspicuous exceptions) diminish vasotone. The vertical position requires sufficient vasotone to keep blood squeezed upward to maintain head cir-

culation. Otherwise fainting results. The hydrostatic load must be overcome. This load is in addition to the vasoconstriction required in the horizontal position. The blood pressure should rise to meet the increased activity and altitude of the erect position. The efficiency of this response to the load is the essence of the test.

The heart-rate increase on rising we have evidence to construe as a secondary factor. Increased heart rate will raise blood pressure, all other things being equal. The accelerator mechanism is put into operation when the pressure tends to fall, thus revealing the weakness of the vasotone effort, and at the same time disguising or cancelling it in part or in whole. It varies. It may be accelerated feebly or markedly. It may be efficient or fail to keep pressure up. Interchangeability with the blood pressure effect is noted. Hence the two factors must be considered.

Behind the vasotone is the sympathetic system. Behind this, are the endocrine, organic and nutritional conditions. Blood ptosis is marked in subadrenalism, characteristically in post-influenza. Blood ptosis is a measure of the degree of the depression of vasotone from constitutional inferiority, prostration, acute or chronic illness. It occurs markedly before acute illness. It disappears on recovery. It marks recuperation. It reveals how tired or sick the patient is. On the other hand there are conditions which directly irritate vasotone and cause splanchnic overtone which are revealed by this test. This has been found in fibroids and abdominal cancer. When present it is notable.

Since blood ptosis occurs in patients with high blood pressure as well as those with low blood pressure, it is probable that the vasotone function which the test measures, is not the same as that mechanism which causes hypertension. This is significant.

Severe chronic blood ptosis has been treated with ephedrin and adrenal extracts with moderate success. Digitalis and squill the author has recently discovered, in some cases at least, obliterate blood ptosis, pegging at the same mark, first the systolic pressures and then later the diastolic pressures.

Comment

These two signs of circulation efficiency are selected because they show themselves to be factors of each other and, to a degree, interchangeable. More recent observers have added or subtracted from this pair of signs. McCurdy[4] (1910) used heart-rate increase alone, Meylan[5] (1913) added heart-rate increase after exercise (hopping), Foster[3] (1914) used heart-rate after exercise (stationary running) and added the element of "pulse recovery", i.e., the number of seconds required to return the pulse to normal rate. Barach[7] (1915) multiplied the sum of the systolic and diastolic pressures by the pulse rate per minute divided by 100 and arrived at an idea of "the cardio-vascular energy". Barringer[8] (1916), following Graupner and others, noted a delayed rise in systolic pressure after exercise (dumbbell swinging) as deficiency in physical conditon. Schneider[6] (1920) added four other elements to the original two, including reclining pulse rate (low is good), standing pulse rate (low is good), pulse rate after exercise (following Foster, McCurdy and Meylan) and pulse recovery (following Foster) bringing into one index the composite value of six somewhat diverse circulatory measurements. His assigning the highest value to the slowest pulse rate is open to the objection that bradycardia not infrequently accompanies serious circulatory insufficiency. In this and other tests, the reaction to exercise, changes in heart rate or blood pressure immediately after exercise or return of

pulse to normal, is an uncontrolled variable. Most of the tests were worked out on college or high school young men or soldiers. A trained soldier with impaired circulation may hop, run or step up on a stool with little effort, while a clumsy laborer or untrained women with excellent circulation may expend many times the effort and get a worse rating. The load is not constant. The difference in field of test is illustrated by the following: Sixty boys after a summer at camp showed an average improvement of all exercise tests but a loss in the blood ptosis test, and incidentally hemoglobin. Athletics and games on the one hand improved the practice element, while late hours, indulgences and sewage-infected swimming pool showed their influence in reduced vasotone. Keeping the exercise and vasotone elements separate permits a greater understanding of the circulation.

The blood ptosis test has been used generally in the hygienic laboratory notably in testing the effects of ventilation, in the study of the condition of athletes and in medical practice with particular reference to a quantitative estimate of sickness and recovery. It offers large service as a method of record and assay in pharmacology, diagnosis and therapeutics.

The Schneider Test of Physical Efficiency

Edward C. Schenider

The test should not be employed to estimate the functional capacity of the heart. The cardio-vascular factors are used merely to give evidence as to the state of physical fitness or efficiency.

The test is based on 6 factors; (*a*) the reclining pulse rate, (*b*) the standing pulse, (*c*) the difference between the reclining and standing rates, (*d*) the difference between the standing rate

and the rate after a standard exercise, (*e*) the length of time required for the exercise rate to return to the normal standing rate, and (*f*) the difference between the reclining and standing systolic blood pressures. Each factor is assigned a maximum value of 3 points. The score made by a patient may be anywhere from a maximum of 18 to a minimum of 11.

The values assigned appear in six sections of the following table (Table 19) as parts *A*, *B*, *C*, *D*, *E*, and *F*. In scoring, Parts *A* and *B*, also *C* and *D*, always must be used together. Thus if an individual has a pulse frequency increase of 15 beats (see Part *B*) on standing and his reclining rate is 60 (see Part *A*), he is graded 3 on his standing increase. If, however, his reclining rate had been 100 then a standing increase of 15 would have been scored 0.

Directions for Making Observations of Test

Preliminary. — Subject reclines for five minutes.

1. Heart rate is counted for 20 seconds. When two consecutive 20-second counts are the same this is multiplied by 3 and recorded.

2. The systolic pressure is taken by auscultation and recorded. Take two or three readings to be certain.

3. The subject then rises and stands for two minutes to allow the pulse to assume a uniform rate. When two consecutive 15-second counts are the same, multiply by 4 and record. This is the normal standing rate.

4. Standing pulse minus the reclining pulse gives the increase on standing.

5. The systolic pressure is taken as before and recorded.

6. Timed by a stop watch, the subject steps upon a chair 18½ inches high five times in 15 seconds. To make this uniform

A. Reclining Pulse Rate		*B.* Pulse Rate Increase on Standing				
Rate	Points	0–10 beats points	11–18 beats points	19–26 beats points	27–34 beats points	35–42 beats points
50–60	3	3	3	2	1	0
61–70	3	3	2	1	0	− 1
71–80	2	3	2	0	− 1	− 2
81–90	1	2	1	− 1	− 2	− 3
91–100	0	1	0	− 2	− 3	− 3
101–110	− 1	0	− 1	− 3	− 3	− 3

C. Standing Pulse Rate		*D.* Pulse Rate Increase Immediately After Exercise				
Rate	Points	0–10 beats points	11–20 beats points	21–30 beats points	31–40 beats points	41–50 beats points
60–70	3	3	3	2	1	0
71–80	3	3	2	1	0	0
81–90	2	3	2	1	0	− 1
91–100	1	2	1	0	− 1	− 2
101–110	1	1	0	− 1	− 2	− 3
111–120	0	1	− 1	− 2	− 3	− 3
121–130	0	0	− 2	− 3	− 3	− 3
131–140	− 1	0	− 3	− 3	− 3	− 3

E. Return of Pulse Rate to Standing Normal After Exercise		*F.* Systolic Pressure, Standing, Compared With Reclining	
Seconds	Points	Change in millimeters	Points
0–30	3	Rise of 8 or more	3
31–60	2	Rise of 2–7	2
61–90	1	No rise	1
91–120	0	Fall of 2–5	0
After 120: 2–10 beats above normal	− 1	Fall of 6 or more	− 1
After 120: 11–30 beats above normal	− 2		

TABLE 19. — Points for grading cardiovascular changes.

the subject stands with one foot on the chair at the count one. This foot remains on the chair and is not brought to the floor again until after count five. At each count he brings the other foot on the chair and at the count "down" replaces it on the floor. This should be timed accurately so that at the 15-second mark on the stop watch both feet are on the floor.

7. Start counting the pulse immediately at the 15 second mark on the stop watch and count for 15-seconds. Multiply by 4 and record.

8. Continue to take pulse in 15-second counts until the rate has returned to the normal standing rate. Note the number of seconds it takes for this return and record. In computing this return count from the end of the 15-seconds of exercise to the beginning of the first normal 15-second pulse count. If the pulse has not returned to normal at the end of 2 minutes re-record the number of beats above normal and discontinue counting.

9. Check up points and enter final rating.

10. Enter history of case, including amount of sleep, amount of smoking, kind of work (outdoor or indoor, active or sedentary, etc.), time since last meal, any personal worries or any pathological condition which might affect the condition of the subject.

The experience of the air service of our army has emphasized the fact that scores of 7 or less are found in the physically unfit. In general, a score of 14 to 18 is excellent, 11 to 13 is very good, 9 to 10 is fair, 7 to 8 is doubtful, and below 7 is unsatisfactory. Scott found that for a patient with a Schneider Index of 7 or less the neuro-psychiatrist would find at least three of the following symptoms; increased psychomotor tension, prolonged secondary dilatation of the pupils, relaxed peripheral circulation, tics and tremors.

It is important to have the patient mentally at ease during the test; the room should be quiet, with no spectators present. The best results are obtained when a quiet conversation is carried on by the patient and observer so that the patient may not have his cardio-vascular reactions disturbed by emotions.

When making the test the time intervals should be adhered to strictly. Counting of the pulse frequency should begin immediately after the exercise ends.

There are a number of things that may be responsible temporarily for a low score. For an hour, and occasionally two hours, the score is lowered by the ingestion of food. The after-effects of physical exertion have lowered it by as much as 10 points and in some instances these lasted for 2 or 3 hours. Smoking, especially in those not accustomed to tobacco, causes a lowering for from 30 to 50 minutes. Even a heavy smoker shows a fall in his score for from 1 to $1\frac{1}{2}$ hours after smoking two cigars. There is also a diurnal change that should be borne in mind that causes the score to be slightly lower during the afternoon than during the morning hours. Schneider and Truesdell found the score rose steadily during the night.

Such temporary and minor indispositions as diarrhea, a throbbing toothache, marked flatulency and the discomfort of indigestion may give a low score. The loss of one night's sleep ordinarily does not lower the score, but the loss of sleep for the greater part of several nights in succession will do so.

The Dwight-Frost Cardio-Respiratory Test[9, 10]

Harold M. Frost

The cardio-respiratory test was developed seven years ago in the search for a method of measuring circulatory efficiency that would be more uniform, better standardized and more

applicable to applicants for life insurance than the current exercise tests. It is based upon the reaction of the circulation to changes of intra-thoracic pressure produced by various respiratory maneuvers. This reaction is interpreted by the resulting fluctuations of systolic arterial pressure and pulse rate.

FIGURE 5. — Cardio-Respiratory Test Apparatus.

The apparatus is portable. It consists of a small spirometer with attached pressure gauge, designed and manufactured by the Taylor Instrument Companies, and of a stethoscope and a blood pressure instrument (see Figure 5). The blood pressure is determined by the auscultatory method.

The technique is divided into nine separate steps. Step I consists of the initial observation of systolic and diastolic pressures and of the pulse rate. In Step II the subject inhales as deeply as possible, maintaining full inspiration for about ten seconds by closing the glottis and allowing chest and diaphragm to relax, thus increasing intra-thoracic pressure. In Step III he exhales to his limit, maintaining full expiration for about ten seconds by closing the glottis and allowing chest and diaphragm to relax, thus decreasing intra-thoracic pressure. In Step IV he blows against the gauge, maintaining a positive pressure of 40 mm. Hg. for about ten seconds, again increasing intra-thoracic pressure. Steps V to VIII, inclusive, are identical. In these the subject blows through the spirometer to his full capacity at a constant pressure of 20 mm. Hg. Step IX consists of the terminal observation of systolic and diastolic pressures and pulse rate.

In each of Steps II to VIII, inclusive, there is a typical fluctuation of systolic arterial pressure. In Steps II and IV it decreases. In Step III it increases. In Steps V to VIII, inclusive, it increases after a rather extensive initial drop. The extent of these fluctuations must be noted as they constitute the most important elements of the reaction: in Steps II and IV, the maximum decrease; in Steps III, and V to VIII, inclusive, the maximum increase.

To complete the observation, any alteration of the clinical signs during or following the test must be noted, particularly any change in the rate, rhythm or force of heart contractions. The systolic pressure must be observed just before the subject performs each of Steps II to VIII, inclusive, in order to determine the actual fluctuation for each step. Note must be made of the vital capacity in each of Steps V to VIII, inclusive.

The data thus obtained is assembled as a permanent record.

For ease in interpretation a special blank is available with a chart upon which the blood pressure observations are plotted. The pressures noted before each step are termed the base-line pressures and are joined to form the base-line curve. The maximum fluctuations of pressure during each step are termed the reaction pressures and are joined to form the reaction curve. The nature and extent of the fluctuations of both these curves are thus evident at a glance. Upon this blank may be entered the initial and terminal pressures and pulse rates, the vital capacity and any other desirable notes.

In the reactions of apparently normal subjects the systolic pressure falls in Steps II and IV at least 10 mm. Hg. below the base-line level and may approximate the level of diastolic pressure. In Step III it increases to a point not greater than 20 mm. Hg. above the base-line. In Steps V to VIII, it increases to points ranging from 20 to 50 mm. Hg. above the base-line. The base-line curve, while it may vary from 10 to 15 mm. Hg. during the course of the test, displays no excessive fall or rise and no marked fluctuation from step to step. Pulse pressure and rate change but little. The vital capacity is well sustained in Steps V to VIII. There is no intervention during or after the test of abnormalities of rate, rhythm or force of the heart contractions; no marked intensification of clinical signs; no development of symptoms of circulatory embarrassment.

Based upon the reaction to the test of some five thousand individuals who presented circulatory impairments of various sorts, certain abnormal elements in the reactions appear to be established[11]. These are: (1) A base-line curve which drops progressively to a point more than 5 mm. Hg. below the initial systolic pressure or which rises eventually more than 10 mm. Hg. above the initial pressure, or which fluctuates markedly

from step to step. (2) A reaction curve which fails to drop in Steps II and IV more than 10 mm. Hg. below the base-line level, or which fails to rise in Steps V to VIII to a point 20 to 50 mm. Hg. above the base-line level, or which rises excessively in these Steps more than 50 mm. Hg., or which shows a progressive tendency to fall away in Steps VI, VII, and VIII. (3) A pulse pressure which at the end of the test has decreased more than 10 mm. Hg. (4) A pulse rate which at the end of the test has increased more than 10 points. (5) A vital capacity which progressively decreases in Steps VI, VII, and VIII.

An inefficient, weak reaction is indicated by various combinations of the dropping base-line curve; the reaction curve which fails to drop sufficiently in Steps II and IV or to rise to a satisfactory level in Steps V to VIII, or which falls progressively in Steps VI, VII, and VIII; the decreased pulse pressure; the increased pulse rate; the decreasing vital capacity. The combination of a base-line curve which rises or fluctuates excessively, of a reaction curve which rises excessively in Steps V to VIII, and of an increasing pulse rate indicates an over-acting, unstable, irritable circulation. In addition, the intervention of irregularities of the rate, rhythm or force of the heart contractions, or of symptoms of circulatory embarrassment, or a marked intensification of the clinical signs are considered abnormal.

Basing an opinion upon our experience of the application of the test over a period of seven years and upon over 5,000 applicants for life insurance, it appears that the test is entirely practicable. The fluctuations of systolic pressure are at times rapid and extensive, frequently covering a range of over 100 mm. Hg. It is obvious that the examiner must be adept in the taking of the systolic blood pressure. Perfection of the technique requires a considerable amount of practice. The test does

not demand any undue amount of time, being easily performed in from ten to fifteen minutes. For the subject, it is not objectionable and rarely difficult. It provides a satisfactory measuring rod of the degree of circulatory efficiency existing at the time of the examination. It applies to the cardio-vascular system a load which may be measured approximately and controlled; increased or decreased as the physical condition of the subject may dictate; applied under conditions which would not permit the use of more violent exercise tests. It is possible to repeat it at subsequent intervals under similar conditions with an approximately equal degree of load. Its results may be recorded by graphic method which makes possible not only a rapid and easy interpretation, but an accurate comparison with the results of other tests.

Bibliography

1. Crampton, C. W.: Address, Olympic Congress, St. Louis, 1903.
2. Crampton, C. W.: A test of condition, Med. News, **87**: 579, 1905; Blood ptosis, N. Y. Med. Jour., Nov. 8, 1913 and Am. Jour. Med. Sc., **160**: 721, 1920.
3. Foster, W. L.: A test of physical efficiency, Am. Phys. Educ. Rev., **19**: 632, 1914.
4. McCurdy, J. H.: Adolescent changes in heart rate and blood pressure, Am. Phys. Educ. Rev., **15**: 421, 1910.
5. Meylan, G. L.: Twenty years progress in tests of efficiency, Am. Phys. Educ. Rev., **25**: 135, 1913.
6. Schneider, E. C.: A cardiovascular rating as a measure of physical fatigue and efficiency, Jour. Am. Med. Assoc., **74**: 1507, 1920.
7. Barach, J. H.: The energy index, Jour. Am. Med. Assoc., **62**: 529, 1914.
8. Barringer, T. B., Jr.: Circulatory reaction to gravity test work is a test of the heart's functional capacity, Arch. Int. Med., **17**: 363, 1916.
9. Frost, H. M.: The response of the cardio-vascular system to respiratory exertion, Boston Med. and Surg. Jour., **191**: 853, 1924.

10. Frost, H. M., and Amiral, H. H.: Cardio-vascular function: the response of the cardio-vascular system to respiratory strain as applied by the cardio-respiratory test, Anesth. and Analg., **5**: 113, 1926.

11. Frost, H. M.: The cardio-respiratory test: analysis of experience for the first five years, Proc. Assoc. Life Insurance Medical Directors of America, **14**: 183, 1927.

CHAPTER VI

BLOOD PRESSURE AS RELATED TO LIFE INSURANCE

Harold M. Frost

The medical departments of American life insurance companies were somewhat slow in the full utilization of blood pressure observations as an essential part of the physical examination of applicants for insurance. While they began to give this matter serious consideration about the year 1900, it was not until fully twelve years later that the routine observation of systolic and diastolic pressures had become a general practice.

This was due in part, in the earlier years, to a natural skepticism as to the practical value of blood pressure determinations in the selection of risks, fostered by an apparent crudeness of the technique, by a general ignorance of it on the part of medical examiners and by lack of definite indications as to the probable effect of extensive alterations of blood pressure upon longevity. In the years subsequent to 1911, medical directors, although they began generally to recognize that blood pressure was important, were hindered in the development of its determinations as a routine practice by the lack of equipment and technical training on the part of their examiners.

For some years there was considerable discussion and not much unanimity as to the upper limit of normal systolic blood pressure. According to a variety of opinions, it varied from 145 to 170 mm. Hg. Gradually, with the increase in the mass of determinations, a conception of the average pressures by age

and sex began to crystallize. This is reflected in its most recent and extensive development in the results of the investigation of blood pressure by the joint committee on mortality of the Actuarial Society of America and of the Association of Life Insurance Medical Directors.

This committee analyzed the blood pressure of 596,374 individuals, 545,121 men and 51,253 women, the observations having been made prior to the year 1921. With but few exceptions these were persons representative of the average healthy mass of population. The following average pressures

	Systolic		Diastolic	
Age	Women (Mm.)	Men (Mm.)	Women (Mm.)	Men (Mm.)
20	116	120	77	79
30	119	122	79	81
40	124	125	82	83
50	130	129	85	85
60	134	134	87	87

TABLE 20. — Average blood pressures; life insurance statistics.

were found (Table 20). It is apparent that the pressures of women are less than those of men under age 40, but that thereafter there is but little difference.

Upon the basis of average pressures coinciding approximately with those above, it has been possible to estimate the importance of varying degrees of deviation of blood pressure from the average, particularly of increased pressure. Previous to the year 1911, the few medical directors who were requiring blood pressure readings — in the case of their older applicants or of those applying for large amounts of insurance — had noted an occasional circulatory catastrophe occurring in an applicant

with high pressure within a few months after examination. This was a disturbing fact, but not conclusive.

In the year 1909, Dr. John W. Fisher, Medical Director of the Northwestern Mutual Life Insurance Company, the first to demonstrate in a scientific manner the danger of high blood pressure in the selection of risks, presented the results of his investigation of a few cases showing an excessively high mortality. Two years later he presented additional facts which supported his first investigation in a startling fashion. From a later investigation of 4,165 risks rejected for high blood pressure only, over a period of thirteen years[1], he demonstrated that deaths from circulatory disease and nephritis were far in excess of the average, comprising 71.6 per cent. of the total, and that mortality increased in direct proportion to the degree of elevation of systolic pressure, as shown in Table 21.

Systolic Blood Pressure Mm. above average for age	Mortality	Excess Mortality
10–14	136.1%	36.1%
15–24	183.8%	83.8%
25–34	204.4%	104.4%
35–49	248.5%	148.5%
50 +	414.7%	314.7%

TABLE 21. — Relation between mortality and degree of elevation of systolic pressure.

Investigations of systolic blood pressure by Doctors Rogers and Hunter[2], respectively Chief Medical Director and Actuary of the New York Life Insurance Company and by the Joint Medico-Actuarial Committee previously mentioned, support these observations, as shown in Table 22.

In all investigations, the increase in deaths from circulatory diseases has been marked. It appears from the two latter investigations that high blood pressure is of more serious import

in middle than in early or late life, inasmuch as the mortality in the age group 40–49 is far more excessive than in age groups 15–39 or 50–65.

The effect of increased diastolic pressure, as determined in the investigations of Rogers and Hunter and of the Joint Com-

Systolic Blood Pressure Mm. above average for age	Mortality	Excess Mortality
New York Life Experience, 1907–1922.		
10–25	146%	46%
26–35	188%	88%
36–50	248%	148%
New York Life Experience, 1916–1925.		
15–25	132%	32%
26–35	171%	71%
36–45	210%	110%
Joint Committee Investigation		
1–10	131%	31%
11 +	143%	43%

TABLE 22. — Data of Rogers and Hunter[2] showing relation between mortality and degree of elevation of systolic pressure.

mittee, parallels that of increased systolic pressure. This is doubtless due to the fact that in most instances an increase in both pressures is coincident. The increase in mortality is practically the same; likewise, the increased incidence of deaths from circulatory disease.

With respect to low blood pressure, it appears to have been the constant opinion of medical directors that pressures somewhat below the average predisposed to increased longevity. This opinion is substantiated by the investigation of the Joint

Committee in that systolic and diastolic pressures down to a point at least 10–15 mm. below the average carry a lower mortality than average or higher pressures. The effect of pressures lower than this has not been determined. From the point of view of the most favorable mortality, the pressures 10–15 mm. under the average may be considered the normal.

In summary, the determination of blood pressure has become a routine and indispensable practice in examinations for life insurance. From the mass of material thus obtained an accurate conception has evolved of the average systolic and diastolic pressures at different ages. It is clear that pressures somewhat below the average carry the most favorable mortality and may be considered the more normal. It is even more obvious that pressures exceeding the average are of serious import, carrying not only an increased incidence in deaths from circulatory disease, but also an excessive mortality, which increases in direct proportion to the degree of excess blood pressure.

Bibliography

1. Fisher, J. W.: Risks rejected for high blood pressure only, years 1907–1920, Proc. Assoc. Life Ins. Med. Directors of America, **9**: 63, 1922.
2. Rogers, C. H. and Hunter, A. W.: Mortality study of impaired lives No. 5, Proc. Assoc. Life Ins. Med. Directors of America, **13**: 176, 1925.

CHAPTER VII

THE INFLUENCE OF HABITS AND DAILY ROUTINE UPON BLOOD PRESSURE

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The influence of habits and daily routine upon blood pressure is a very complex subject, and it is impossible to discuss it in great detail. Those aspects have been chosen which, at the present time, are regarded as having a direct bearing upon hypertensive states. The most effective treatment of hypertension is based on a knowledge of the influence on blood pressure of the everyday occurrences in life.

Variability of Blood Pressure — "Spontaneous Variation"

There is no doubt that blood pressure varies greatly in practically all people, not only from day to day, but from hour to hour and even from minute to minute. Tixier[1] found that it was rare for the blood pressure to remain constant as long as five minutes. The rise and fall is much more marked in the systolic than in the diastolic figures. Patients with hypertension exhibit much greater variations than those with a normal pressure. The designation "spontaneous variation" of blood pressure perhaps is justified, since the changes in the arterial tension accompany routine emotions and acts. It is very important for the physician to be on the alert for this "spontaneous variation" because a correct interpretation of blood pressure readings and the proper treatment of hypertensive cases cannot be achieved without due consideration of this factor. The facts are so patent that most observers take them for granted, and yet many articles on blood pressure are worthless because the possibility of "spontaneous blood pressure variations" was disregarded. The variations ordinarily found may come under three heads; (1) those associated with emotional stress or nervous relaxation, (2) those brought about by rest, and (3) those due to vasomotor spasm.

Emotional Stress

The effect of any emotional stress is to elevate the blood pressure. The response of the vasomotor system in different persons of course varies greatly; it may be very slight, though frequently it is marked. Some authors have given an overresponse to nervous excitement the designation, "vasomotor

neurosis". Gumprecht[2], as early as 1900, noted how a student when watching blood pressure determinations upon himself always registered 15 mm. higher than when he did not; after quarreling, a rise of 30 to 40 points was common; a patient having a systolic blood pressure of 170, had one of 202 after a successful hand at cards, and in another the figure rose from 156 to 172 on being amused and laughing. O'Hare[3] in his experience found that excitement always caused a sharp rise in systolic pressure (as high as 52 mm. of mercury) and a more moderate rise in diastolic pressure (as high as 24 mm.). Mosenthal and Short[4] studied one patient whose blood pressure was at a level of 242/116 while he was relating an unpleasant incident, whereas five minutes later the considerably lower reading of 194/114 was obtained. Maloney and Sorapure[5], and later Grossman[6], showed how relaxation brought about by breathing exercises and passive motion lowered the blood pressure; they believe that these measures tend to moderate the effect of the psychic influences responsible for the vasomotor stimulation and consequent increase in blood pressure. In one of their cases the systolic pressure dropped from 215 to 154. Any number of findings similar to the above could be quoted.

Less spectacular are the instances in which the blood pressure varies but slightly from the normal; yet such readings are difficult to interpret because it is not clear whether they are to be regarded as signs of an incipient essential hypertension. This matter has been taken up already in the chapter on normal blood pressure; it may be worth while to give another opinion upon it here: Diehl and Sutherland[7] in examining over 5,000 male college students found that only 15 per cent. of those with pressures of 140 mm. or more on first examinations showed continued elevation on later tests. These authors believe that most

of the readings of 140 mm. or more were due to nervousness, and that when this factor was eliminated, very few cases of hypertension remained.

Similar observations are well nigh universal. Thus great care must be exercised in interpreting the first few blood pressure readings in any patient too literally. The following table

Date	Blood Pressure	
	Systolic	Diastolic
1925, October 9	192	110
14	194	106
21	204	106
28	196	99
November 5	188	87
19	169	81
December 4	154	74
1926, April 12	162	78
30	150	94
1927, February 4	148	80
April 27	142	76

TABLE 23. — Mrs. T. L., aged 68, had had hypertension for some time past and had been treated by a member of the family. When the medical responsiblity was transferred to another physician, the blood pressure diminished in a satisfactory way. No other therapeutic measures of note were instituted. Approximately one month elapsed before the blood pressure began to diminish (Mosenthal[8]).

(23) shows how a full month may be required before the blood pressure assumes its characteristic level, which Tixier[1] has aptly termed the "residual blood pressure". Such cases as detailed in Table 23 render it clear that long control periods are necessary before any experimental observations on the effects of therapeutic measures designed to lower blood pressure can be interpreted successfully.

Rest

Rest has a marked lowering effect on blood pressure. To a

certain extent this is accomplished through relief from emotional and nervous strain and, therefore, may be considered as part of the preceding section; from the therapeutic standpoint, however, it represents another means of bringing about a drop in arterial tension and consequently merits further consideration.

Addis[9] describes the marked differences in pressures and pulse rate occurring during the "basal state", that is, while fasting and at absolute rest, from those under "day-time" conditions, when the subject has taken food and is up and about. These results are remarkable in showing the enormous effects that may be accomplished by comparatively simple measures and again accentuates the value of "sleeping cures" advocated by Blume[10].

There are many observations indicating that short periods of rest afford considerable relief from hypertension; thus Mosenthal and Short[4] in 49 consecutive hypertensive dispensary patients noted, as the result of rest, a drop of systolic pressure of 10 to 44 mm. in 38, or more than 75 per cent., whereas in the remaining 11 subjects the blood pressure changes were negligible. That short periods of rest are of considerable value in relieving the body from the strain of a high blood pressure may be gathered from the fact that in 80 per cent. of the cases the lowest pressure was registered within a half hour or less after the rest was begun. This lower level of blood pressure was maintained in many instances for an indefinite period after the upright position was resumed.

A longer period of relaxation results in a greater drop in arterial tension. This may be gathered from Addis'[9] observations in comparing basal and day-time pressures and is a uniform experience in hospital patients whose blood pressure is read daily. The subsequent course of the blood pressure in these cases is often lower than before the enforced rest; at other

times it resumes its former level with discouraging rapidity. There is one particularly interesting case reported by Dawson[11] in this connection: A girl, aged 23, whose only complaints were slight fatigue and some dyspnea on heavy exertion, showed a rest pressure of 250/150, after exercise 280/150; a month's rest in bed lowered the systolic pressure to 165; when she left

Conditions	Systolic Pressure	Diastolic Pressure	Pulse Pressure	Pulse Rate
Basal	99	71	28	63
Day Time	127	78	50	80

TABLE 24. — Average observations on normal persons (Addis)[9].

	Basal				Day Time			
Case	Systolic	Dia-stolic	Pulse Pressure	Pulse Rate	Systolic	Dia-stolic	Pulse Pressure	Pulse Rate
1	170	105	65	64	223	115	108	96
2	140	90	50	96	155	80	75	122
3	133	77	56	80	164	78	86	93
4	118	73	45	80	164	99	65	91
5	130	80	50	60	156	90	66	91
6	120	85	35	60	168	95	73	86

TABLE 25. — Basal and day-time pressures and pulse rates in cases of essential hypertension (Addis)[9].

her bed and took a ten minute walk the systolic pressure rose to 215. Even so, there was the distinct advantage of a month's respite from the terrible vascular strain of an excessive hypertension.

Vaso-motor Spasm

Vaso-motor spasm of unknown origin occurs in some individuals; this is prone to be habitual and manifests itself in the

same person at more or less frequent intervals. These patients are the subject of intermittent claudication. Examples of this sort are given and discussed in the chapter on types of hypertension.

Sleep

It is known that blood pressure diminishes during sleep. Blume[10] observed an average drop of 15 mm. in men and 21 mm. in women who had a normal day pressure; when the latter was high, the difference averaged 31 in men and 39 in women. Brooks and Carroll[12] recorded a lowering of 24 mm. during sleep, when the usual pressure was between 110 and 170, when it was below 110 a drop of 16.5 mm. occurred, whereas in hypertensive cases with an arterial pressure above 170 the diminution was as much as 44.8 mm. The drop in arterial pressure during sleep, if the day time level is higher than normal, apparently varies in different individuals. Thus Campbell and Blankenhorn[13] found in 36 cases of hypertension that there may be a satisfactory lowering of the pressure, or only a slight drop, or no diminution at all. They make the interesting observation that patients, whose blood pressure falls to normal during sleep, showed less evidence of disease and less disability than those who maintained an elevated arterial tension.

The greatest drop in blood pressure, according to Brooks and Carroll[12], occurs one to two hours after going to sleep; Campbell and Blankenhorn[13] believe this to take place in four hours. However, there is a general agreement that no further lowering of the blood pressure takes place after the maximal drop; the majority of observers believe that the minimal figures persist with little variation during the remainder of the night. The diminution in arterial tension takes place only during the longest

sleep in the 24 hours; repeated naps do not bring about a recurrence of the hypotension, at least not to the same extent. The usual drop in the blood pressure characteristic of sleep could not be increased by the administration of chloral hydrate in 3.3 gm. (50 grain), or potassium bromide in 8 gm. (120 grain) dosage. (Brooks and Carroll[12].)

It is important to note that restless sleep does not result in a reduction of arterial tension. In fact, MacWilliam[14] demonstrated that during exciting dreams the systolic pressure rose from 125 and 130 mm. to 182 and 200 and the diastolic from 75 to 105. Krumbhaar[15] believes this may be the cause of spontaneous rupture of the heart during sleep; it is tempting to add, of angina pectoris, nocturnal paroxysmal dyspnea and apoplexy, as well.

Katsch and Pansdorf[16], as the result of their observations, suggest the possibility of "sleeping cures" for hypertension. This certainly is an eminently desirable form of treatment. In carrying it out the aim should be that the patient not only goes to bed, but that he sleeps and that he has a restful sleep, free from exciting dreams. The regulation of diet, intestines, occupation, amusements, etc., in this regard have an obvious bearing. Sedatives and hypnotics in suitable cases are of inestimable value. Even if large doses of bromide and chloral do not help to lower the pressure in the patient whose slumber is peaceful and normal, these drugs will accomplish such a result in the restless sleeper and in the victim of nightmares. Bromides, chloral, barbital, phenobarbital, etc., are all excellent; some patients react better to one than to the other, and the adjustment of the drug in each case is a matter for study. The medicines may be given in a single dose at bed time, but in other instances a distribution of fractional amounts three or four times

during the day paves the way for good deep sleep and serves to banish harassing dreams.

Exercise — Physical Exertion

As a rule, the immediate effect of physical exertion upon blood pressure is to raise it. The changes in the arterial tension vary with the amount and intensity of the exercise and also, to a a great extent, with the physical training of the individual. In brief (for literature and detailed discussion see Wiggers[17] and Meakins[18]) it may be expected that for as long as 25 minutes after beginning exercise the systolic pressure will rise as much as 60 or 70 mm., the diastolic 40 mm. This increase in the arterial tension must not be regarded as an isolated phenomenon but as part of the response to the increased need for oxygen during muscular work. The other factors are an increased minute discharge from the ventricles, effected by an accelerated heart rate, an augmented systolic discharge, dilatation of the capillaries of the muscles and possibly a constriction of the visceral arterioles, serving to divert blood from the liver and other internal organs to the heart and muscles.

A hasty consideration of these facts may lead to the conclusion that unnecessary physical activity should be shunned by the hypertensive patient. A rise in blood pressure, an increased circulatory rate and an accelerated heart beat are undesirable, theoretically at least, where the heart and blood vessels are to be spared as much as possible. However, we may recall here the observation of Aubertin and Coursier[26], mentioned in the section on weight, that among overweight individuals the sedentary person is more subject to an excessively high blood pressure than the active individual. Furthermore, it has become evident that the hypertensive patient carries on better

and longer with judiciously controlled exercise than without it. Similar conclusions have been reached in regard to myocardial failure. To a great degree certainly the treatment of hypertension centers on maintaining the efficiency of the heart, and the principles and methods used in the treatment of cardiac disease are applicable here. Since the heart muscle in the majority of cases of hypertension is normal, except for hypertrophy, it responds much more readily to physical training than in a "cardiac case" with its usual attendant myocardial degeneration. Furthermore, the maintenance of the characteristic blood pressure of any individual, whether the level be high, normal or low, must be regarded as a function carried out not only by the heart, arteries, capillaries and veins, but to a certain extent by the other tissues as well; it is the expression of the body as a whole, like the temperature, the secretion of urine, the metabolism of glucose and other vital processes. One of the essentials in keeping the organs that contribute to blood pressure regulation functionally effective is physical exercise. Precisely how it acts is not entirely clear, but judging from results, most clinicians are satisfied that it not only does, in the long run, lower blood pressure, but that it also puts the patient in a more favorable condition to withstand the wear and tear that a high arterial tension imposes. Exercise should never be carried to extremes so as to produce great fatigue or dyspnea of any moment. Walking and resistance exercises, suitably graded for each patient, can be taken advantageously by nearly all. Golf, horse-back riding and more active sports, such as tennis or swimming, are not out of place provided the heart is not overtaxed thereby, and the blood pressure is not sufficiently elevated to make a cerebral accident probable. Physical effort should be planned to constitute a long steady course of training

rather than short, intermittent, competitive exercise. In advising exercise the presence of coronary disease or other complications of hypertension must be considered.

Weight

This subject is associated intimately with that of over-indulgence in starches and fats. Herrick[19] stresses obesity, hypertension, arteriosclerosis and a high blood sugar as a definite clinical entity; the hyperglycemia was not found in thin persons with an elevated blood pressure. In the patients that Herrick[19] describes the reduction of carbohydrate food not only often results in loss of weight and a lowering of the blood suger, but also in a return of the blood pressure towards normal values. A faulty diet, wherein sugars and starches without stint take the place of proteins, would seem to be the keystone in this pathological structure.

The influence of overweight on blood pressure possibly has been somewhat exaggerated. There are certainly very many obese individuals whose arterial tension is not above the average for their age. The tables of Symonds[20] (Tables 26 and 27) would indicate only a rise of about 8 mm. for the 50 per cent. overweight group. This is a comparatively small difference. These tables may be of some help as a guide to normal or usual blood pressures in over- or underweight individuals, and any rise above these figures may be regarded as due to other causes.

Huber[21], in studying 1,332 army officers and officials of the southeastern part of the United States, found that 49 per cent. of those that are more than 10 per cent. underweight have subnormal blood pressures, while only 18 per cent. of those overweight show hypertension; of subjects with a systolic pressure

of 140 mm. and higher, 22 per cent. were underweight and 14 per cent. overweight; whereas in those whose systolic blood pressure was below 110 mm., 53 per cent. were underweight and

Ages	About 35% underweight	About 20% underweight	Normal	About 30% overweight	About 50% overweight
From 15–19	114	120	123	128	131
20–24	117	121	123	128	131
25–29	117	121	124	128	131
30–34	118	121	124	129	132
35–39	118	122	124	129	132
40–44	119	123	126	130	133
45–49	121	125	127	132	135
50–54	123	126	130	134	137
55–59	126	129	133	138	140
60 and over	128	132	135	139	142
All ages	120.1	124.0	126.9	131.5	134.4

TABLE 26. — Systolic pressure for men (Symonds)[20].

Ages	About 35% underweight	About 20% underweight	Normal	About 30% overweight	About 50% overweight
From 15–19	75	77	79	82	84
20–24	76	78	80	83	85
25–29	77	79	81	84	86
30–34	78	80	81	85	87
35–39	79	81	82	86	88
40–44	79	81	83	87	89
45–49	80	82	84	87	89
50–54	81	83	86	88	90
55–59	82	84	87	89	90
60 and over	82	85	87	89	90
All ages	78.9	81.0	83.0	86.0	87.8

TABLE 27. — Diastolic pressure for men (Symonds)[20].

6 per cent. overweight. These observations would indicate a rather casual relationship between weight and blood pressure. As Huber[21] notes, these results are somewhat at variance with the data of Siler[22] for army officers in the Philippines and the

report of the annual army officers' examination in 1923[23], both of which point to a significant correlation between underweight and low systolic pressure on the one hand, and overweight and high systolic pressures on the other. Dunham's[24] findings in healthy army officers coincide with those of Siler[21].

Fisk[25] suggests that, besides overeating, lack of exercise in the obese is a cause for the tendency to a rise in blood pressure. His figures bring out the fact that a certain number of stout individuals have a normal blood pressure and that there are likely to be fewer such as the weight increases. Fisk's[25] observations are as follows:

Overweight 10–15 per cent.

18 per cent. had increased blood pressure as compared to normal.

Overweight 15–20 per cent.

26 per cent. had increased blood pressure as compared to normal.

Overweight 20 per cent. and over.

78 per cent. had increased blood pressure as compared to normal.

Aubertin and Coursier[26], in a very suggestive study, have elaborated the relation of sedentary habits (or lack of exercise), obesity and blood pressure. They compared 70 obese institutional inmates with 24 overweight persons who were leading an active life. Of the sedentary individuals only 10 per cent. had a normal pressure, while of the active ones 62.5 per cent. showed no rise of arterial tension. These observers reject the assumption that obesity alone may be responsible for hypertension. This leads to the idea that physical activity, in spite of raising blood pressure temporarily, furthers the normal control of vascular tension by maintaining the functions and tissues at a better level of physiological efficiency.

In the experience of some clinicians (Terry[27], Fisk[25], Rose[28]) uncomplicated hypertension, that is essential hypertension, often may be controlled in the obese by weight reduction; others have not been so successful in this respect (Allen and Sherrill[29], Fahr[30]). My own experience in this matter has led me, more recently, to believe that lowering the weight does not, in itself, have very much effect on the blood pressure. A conclusive study has not yet been made on this important subject.

However the indications for clinical procedure, fortunately, are clear cut, for, no matter what our views may be in regard to the relation of weight to blood pressure, there can be no doubt that it is exceedingly important in treating hypertensive patients to prevent overweight and, when obesity exists, to attempt reduction to normal weight. From a study of prognosis it is known that cardiac failure is the most frequent of the serious sequels of a permanently elevated blood pressure; every pound of weight of course adds to the heart's physical burden and favors myocardial insufficiency.

Diet

Proteins

The idea that proteins elevate the blood pressure, at least during short periods of indulgence, has been definitely done away with (Mosenthal[31], Squier and Newburgh[32], and Strouse and Kelman[33]). In regard to the influence of prolonged unrestricted protein feeding, there are no observations available indicating that blood pressure is increased thereby. In spite of this, a very widespread belief, amounting to a conviction, exists in medical as well as non-medical circles that proteins, especially meats and particularly red meats, raise arterial tension. There are two observations that serve to throw some

light on this problem. One is that of Lieb[34] which showed that Stefansson, the arctic explorer, aged 43, had lived for a number of days, totalling nine years, on an exclusive meat diet, and that at the end of that time he was in good condition, with a blood pressure of 115 systolic and 55 diastolic. The other publication on this subject is that of Thomas[35] who finds that the Greenland Eskimo, on a purely carnivorous diet, exhibits no increased tendency toward vascular hypertensive and renal disease. A very low protein diet induces anemia and physical weakness (Benedict[36]). The statement, therefore, seems warranted that all forms of protein, whether from fish, red meat or white, eggs or any other source, are permissible in the usual amount; if the hemoglobin and red blood cell count rise above the normal, the proteins should be curtailed, and only then. In the event of the existence of nephritis, the proteins in the food must be restricted in direct ratio to the rise in the blood urea; the presence of albuminuria in itself is of no more value as a guide than is the blood pressure.

Date 1927	Blood Pressure		Weight Pounds	Hemoglobin per cent.
	Systolic	Diastolic		
May 11	162	91	150	66
27	180	118	152	73
July 11	198	118	155	
27	175	106	157	
October 1	206	118	157	
7	177	106	157	78

TABLE 28. — Male, aged 50, 33 pounds underweight for height and age, malnutrition and hemoglobin of 66 per cent.; the blood pressure rose as nutrition improved; results mainly attributed to an increase of protein in the diet (Mosenthal[8]).

How quickly the blood pressure rises in a case of malnutrition as the general condition is improved is shown in Table

28. The patient had been given an extremely low protein diet for a long time, and as a result he had developed a secondary anemia and marked lassitude and weakness. The addition of proteins to his diet remedied these symptoms, but at the same time elevated the blood pressure. A necessary choice must be made between two evils under these circumstances, and the physician perforce must be the judge of the best course to pursue.

There is a serious aspect of high protein feeding in the production of an excessive number of red blood cells and increase in the hemoglobin; Dr. Benjamin Ashe, after reviewing recently a considerable number of cases of hypertension, called my attention to the erythremia existing in those patients that had suffered from apopleptic seizures, whether mild or severe. It is true that protein food has the effect of increasing the hemoglobin and the red blood cells; consequently, the proteins should be restricted in cases of hypertension having a plethoric tendency, but only in them; there is no reason to curtail meats, etc., as a routine measure.

The danger for the hypertensive patient, whose protein ration is curtailed, lies in the fact that he is encouraged to replace them with fats and especially with starchy foods, thus bringing on a gain of weight and often a marked obesity; this constitutes the gravest error in the treatment of hypertension. For a more detailed discussion of this problem the reader is referred to the section on weight in this chapter.

Carbohydrates

In the treatment of hypertension and many other conditions, such as arteriosclerosis, it has been common practise to advise the substitution of starches for the foods high in protein con-

tent, especially meats. This switch in the quality of calories neither lowers nor raises blood pressure appreciably; the later effects of such measures may be obesity, anemia and an elevation of blood sugar. It is only through these less immediate results that the carbohydrates influence blood pressure; since hypertension is a disorder affecting the body not for a short time, but for many years, such indirect consequences of indulgence in starchy foods must be seriously considered. The relation of weight to blood pressure is discussed in a separate section.

Blood Sugar. — Fluctuations in glycemia, whether slight, or marked, as in diabetes mellitus, whether of long or short duration, apparently do not influence blood pressure (Mosenthal[37]); a very marked reduction of blood sugar, as occurs in the hypoglycemic reaction after an overdose of insulin, is accompanied by a distinct increase in blood pressure. Wilder[38] reports such a case, where the systolic pressure rose as high as 220 although the normal arterial tension did not exceed 120. This rise in pressure is attributed to the liberation of epinephrine, a spontaneous attempt at the restoration of normal blood sugar. Neubauer[39] in 1910 advanced the hypothesis that the simultaneous occurence of hypertension and hyperglycemia was brought on by an increase in epinephrine. This is theoretically possible but lacks confirmation in the absence of suitable methods of studying the adrenal gland and its secretion.

Another aspect of this problem leads us to the question whether hypertension may not, under the circumstances, cause hyperglycemia. There is no relation of immediate cause and effect; this can be appreciated readily from the fact that in less than half of the cases of hypertension, reported by various authors, is there a rise both in blood pressure and blood sugar.

However, a persistently elevated arterial tension will result in a widespread arteriosclerosis which may involve the pancreas among other organs. Upon this idea O'Hare[40], Kylin[41] and Botti[42], when they find a diminished carbohydrate tolerance in hypertensive patients, base the statement that these are instances of potential or pre-diabetes, that is, of incipient pancreatic lesions. This is very plausible and may account for the slightly increased frequency of hypertension among diabetics (Kramer[43]); in other words, a persistently increased blood pressure may be the cause of arteriosclerosis which, in turn, may bring about pancreatic degeneration and diabetes.

Fluid Intake

The amount of fluid intake is supposed to influence arterial tension by changing the blood volume; the effect of variations in blood volume has been discussed in Chapter I. The actual results of the drinking of large amounts of fluid may be considered under two heads: (1) The swallowing of enormous quantities (10 liters more or less) which, according to Miller and Williams[44], raises blood pressure. (2) The taking of more moderate amounts of liquid, such as would come into consideration under normal circumstances; no increase in arterial tension was found with the drinking of 1 to 6 liters of water a day (Orr and Innes[45]); there was no change in either systolic or diastolic pressure after 1 or 2 bottles of beer (Engelen[46]); about $1\frac{1}{2}$ liters of water did not increase the blood pressure in normal individuals, but did elevate it in patients with acute nephritis and arteriosclerosis (Dorner[47]). Summarizing the situation, it may be concluded that fluids in the usual amounts and even considerably above these limits, up to about 6 liters, may be taken without effecting any appreciable change in blood pres-

sure. It is possible that, if myocardial insufficiency, even of slight degree, exists, it is advisable to curtail the liquid intake; this subject will be elaborated under the section on sodium chloride in the next paragraph.

Sodium Chloride

The causal relation of sodium chloride to hypertension has been urged for some time. In 1904 Ambard and Beaujard[48] claimed that there was a direct relation between retention of sodium chloride and the level of arterial tension. In 8 cases of nephritis studied by them, 6 cases conformed to their theory, and 2 did not. These two exceptions are notable; in the first, no rise in blood pressure occurred in spite of a retention of 60 gm. of salt and an accumulation of 5 kg. of edematous fluid; in the second, the blood pressure rose in spite of the elimination of large amounts of previously retained salt. Subsequently Ambard[49] reiterated his views and defined them a little more closely by expressing the belief that all hypertension is due to retention of sodium chloride, and that every case of permanently increased blood pressure is due to nephritis. Today it is firmly established that a permanent rise in arterial pressure is very often not associated with a nephritis. Loeb[50], in regard to this problem, makes the obviously true, but very significant statement that those forms of nephritis, the parenchymatous, that are characterized by a retention of sodium chloride, do not as a rule have a high blood pressure. During more recent years very little evidence has been presented to show that sodium chloride retention or its toxic effect is responsible for the hypertension so characteristic of Bright's disease. But even if the administration of salt in nephritis will not bring about an elevation of blood pressure, it may induce other effects that are fraught with

danger. The doctrine that sodium chloride is the cause of an elevated blood pressure is largely the result of the confusion of uremic symptoms and those of myocardial insufficiency with hypertensive disease.

Combe[51] quotes an interesting observation of Castaigne, that injections of sodium chloride may produce fatal uremia in "chronic atrophic nephritis"; Munk[52] noted a somewhat similar instance after the administration of a fairly large dose of salt. Mosenthal and Short[4] had a nephritic patient, who developed a severe attack of angina pectoris after a 10 gm. dose of sodium chloride. After a few days' use of salt, in one of my cases with impaired renal function, a typical uremic state developed which promptly disappeared when the salt was discontinued. However, in individuals with a normal kidney function, salt in similar amounts produced no manifestations whatever, except occasional nausea, which would not be unexpected after a 10 gm. dose of sodium chloride. When renal insufficiency exists, therefore, salt should be administered very cautiously.

In arteriosclerosis, Bayer[53] and Lowenstein[54] failed to find any relation between sodium chloride ingestion or retention and blood pressure. In 1920 Allen[55] made very strong claims for the specific relation between salt and hypertension. These have been reinforced by subsequent publications[29, 56]. One of the original ideas, namely that the concentration of salt and level of blood pressure parallel one another, has been discarded and requires no further comment. The "unitarian doctrine of hypertension" depends upon the idea that salt, when retained in the body, raises arterial pressure. This can be controlled, according to Allen[29], by restricting the salt in the diet. The curtailment of sodium chloride must be very strict so that only 0.5 gm. is eliminated in the urine in 24 hours; if immediate

results do not follow, the dietetic restriction must be carried on for an indefinite period and may have to be continued subsequently to maintain a lowered blood pressure. Blaisdell[57], Higley and Field[58], Houghton[59], Konikow and Smith[60], Musser[61] and Stone[62] endorsed the results of Allen and his co-workers, while Christian[63], McLester[64], O'Hare[65], Strouse[66] and Mosenthal and Short[4] failed to find the expected relation between salt and blood pressure. The cases published by Allen[29] lack sufficiently long control periods to make them convincing. As mentioned under "variability of b ood pressure", in this chapter, many blood pressure determinations, covering a period of at least several weeks, are required to determine the characteristic arterial pressure of any individual. Until this is established, observations on the effectiveness of any therapeutic measure, designed to influence blood tension, lack a base line. This important matter has been overlooked in Allen's and many similar studies and robs them of much of their value. I have seen a number of hypertensive patients, whose blood pressure was reduced by a salt restriction combined with sanatorium treatment, only to rise again after they returned to their usual occupations, in spite of the fact that the prescribed diet was maintained.

A close scrutiny of the protocols of Allen and Sherrill[29] makes it clear that many of their cases show decided symptomatic improvement in spite of the lack of a corresponding change in the blood pressure. This may be attributed to the lifting of the burden which sodium chloride throws upon the heart. In myocardial insufficiency, the output of salt becomes very much diminished (Mosenthal[67]); furthermore, Hartwick and May[68] find that, as the result of a salt free diet, a drop in blood volume of considerable proportions may occur, though this is

not true in every instance. The cardiac complications of hypertension, palpitation, dyspnea, angina pectoris, edema, anasarca, improve remarkably with salt-free diets; if such symptoms exist, this treatment should be rigorously insisted on.

The finding of Soule, Buchanan and Darrow[69] in this connection may be of some interest. These investigators showed that during fever, which is characterized by a subnormal blood pressure, there is an increase in blood volume and a retention of chlorides. Apparently in some, possibly in most conditions, a holding back of sodium chloride in the human organism does not elevate the blood pressure.

In describing his treatment of arterial hypertension, Allen[29] stresses the point that the diet must be supervised more carefully than is customary. It is regarded as satisfactory only when the urine contains 0.5 gm. of chloride or less a day. To accomplish this, foods of very low salt content must be chosen from appropriate diet tables, and no salt whatever must be added during the cooking or at the table. He finds that most of the hypertensive patients stand this restriction very well, and that such a restricted diet may be maintained indefinitely. Because of the occurrence of "privation symptoms" in a comparatively few instances, or because the blood pressure in some patients is not sensitive to a certain amount (to be determined for each individual) of sodium chloride, a weighed quantity of extra salt appropriate for each case was measured out in the morning to be used as desired throughout the day. As a rule, only one to three grams of salt were considered permissible or necessary.

It requires great dietetic skill to carry out these comparatively simple instructions. The so-called "salt-free dietary" in hospitals usually contains 2 to 3 gms. of sodium chloride a

day, and while it meets many therapeutic indications, does not satisfy Allen's criteria. Proteins, carbohydrates and fats, in this regime, should be apportioned so as to meet other demands, e.g., obesity, diabetes mellitus, normal caloric requirements, etc.; consequently no rules can be formulated in regard to them. Allen does not believe these considerations to be of importance in directly controlling hypertension. Finally, it may not be out of place to repeat that when these strict salt-free diets are prescribed, the patients must be watched carefully so that excessive prostration may be forestalled.

Intestines

Gaseous distention or overloading of the intestinal tract may push the diaphragm upward and embarrass the action of the heart; a bowel movement that requires a long, straining effort may be provocative of a cerebral vascular lesion; these are mechanical effects that should be avoided at all costs in hypertensive patients, and their remedy by suitable diet, catharsis, intestinal disinfection, exercise, etc. is obvious.

The theory of the absorption of toxines from the intestines, "autointoxication" or "intestinal toxemia", as a cause of elevated blood pressure, is widely subscribed to. A single dose of blue mass or calomel or castor oil given once or repeated at weekly or monthly intervals, has been advocated often as a means of combatting hypertension. Such catharsis may be beneficial, though its exact value is difficult to define. As a matter of fact, the intestinal intoxication theory rests on hypothetical grounds only. The observations of Alvarez, McCalla and Zimmerman[70] give this idea a stiff jolt. They find that constipation in men has no effect on blood pressure and in women is associated with a lowered pressure, and they con-

clude that the conception of "intestinal autointoxication" as a cause of hypertension is erroneous. Fisk[25] concurs in this view. Thus rectal irrigations and other procedures intended to clean out the alimentary tract are of comparatively little value in most hypertensive patients; they should be resorted to only when there are especial indications for them.

Climate

It has been customary to accredit to hot weather and tropical climates the power to lower blood pressure. Clifford Allbutt[71] quotes Oliver as stating that in continuously hot weather blood pressure is reduced. I have noted, in a few hypertensive patients, a considerable fall in arterial pressure on very hot days. However, there is no conclusive evidence on this point.

Reports on the blood pressure characteristic of peoples in various climates have begun to accumulate and are suggestive in many ways. The Chinese, according to Cadbury[72] and Foster[73], have a lower blood pressure than Europeans or North Americans; furthermore, essential hypertension is virtually unknown among them, and hypertensive nephritis is rare. In India the average systolic blood pressure of the Hindus is about 100 mm. of mercury, while that of Europeans in Bengal is 115 to 130 mm.; regarding the Filipinos there are conflicting observations, some records showing a blood pressure lower than that of the white races while others do not (for references, see Foster[73]). Ismail[74] shakes our faith in the efficacy of treating hypertension by change of climate, when he reports that chronic primary hyperpiesis is common in Egypt and forms at least 10 per cent. of all cases in private clinics, but is rare in hospital practice. It is somewhat surprising to note the finding of Thomas[35] that the Greenland Eskimo has no tendency to hypertension.

The above facts seem to point to the conclusion that climate in itself exercises no controlling influence upon blood pressure, but suggest that inherited characteristics are the dominating factors.

Will tropical or sub-tropical climates reduce hypertension? This question is very important from the therapeutic point of view and yet admits of no definite answer because of the very conflicting and meagre evidence in regard to it. Reference is made to only a few representative opinions on this matter. Roddis and Cooper[75] express the prevalent idea on this subject, when they claim that the systolic and diastolic blood pressure averages 10 to 15 mm. lower in the tropics than in the temperate zone. Foster[73] quotes a communication from Mr. E. F. Harris, Manager of the North China Division of the Sun Life Insurance Co., Shanghai; this statement deserves especial attention, coming from the representative of a life insurance company, which presumably has the means as well as the desire to arrive at the facts; in part the quotation reads: "In our experience the blood pressure of the Chinese is considerably lower than the blood pressure of the Caucasian races. The blood pressure of the white races, i.e., Europeans and Americans in China is, however, in our experience just the same as the blood pressure of such races in Europe and America. We also are of the opinion that hypertension in foreigners is just as common in China as in Western countries, but that hypertension is rare in Chinese." An interesting middle course between two previous opinions is taken by Huber[76], who says that the effect of the tropics is to lower normal or subnormal blood pressures rather than high ones.

This discussion leaves the problem in an unsatisfactory state as regards the direct effect of warm climates upon blood pres-

sure; when southern journeys are considered as a therapeutic measure the probable effect of the climate on the heart, nervous tension, nutrition, etc., as well as on the hypertension per se, deserves the most minute consideration.

Alcohol

There is no unanimity of opinion as to the effect of alcohol on blood pressure. Toxic doses in animals lower blood pressure; it is doubtful whether this is the case with the amounts taken by human beings. In at least two heavy drinkers of whiskey I have seen the blood pressure drop remarkably when they went on the "water wagon". If we accept the statement of Sir Clifford Allbutt[77] that: "it seems now to be generally agreed that mere alcohol is, as such, no cause of hyperpiesis", there still remain the secondary effects to be reckoned with. Alcohol is a food of high caloric value, also an appetizer, and consequently is prone to lead to obesity; when taken in large amounts it brings about fatty degeneration of the heart and muscles and may lead to deficient cardiac power through loss of tone and consequent dilatation (Wiggers[17]). On the other hand, small amounts of alcohol presumably are oxidized completely, act as tonics, increase the appetite, relax excessive nervousness and may be of inestimable value except in those patients in whom a gain in weight is undesirable.

Tobacco

The effect of smoking on blood pressure has been the subject of many investigations. However, many of these observations are not very helpful to the therapeutist, who is concerned chiefly with the results of the excessive and prolonged, habitual use of tobacco, and such studies cannot be carried out on ani-

mals, nor have they been made on human beings except in an incomplete fashion.

The blood pressure after short periods of smoking apparently reacts in various ways. Lee[78] tabulates the following observations on the blood pressure of persons who inhaled while smoking:

Novices	rise of systolic pressure				10–20	mm.	Hg.
Moderate smokers	"	"	"	"	10	"	"
Excessive smokers	"	"	"	"	2–4	"	"

Rolleston[79] finds that smoking raises the systolic blood pressure 5 to 20 mm., the diastolic pressure being less influenced, and that the pressure falls to normal or below within half an hour. Cook and Briggs[80] note a greater rise (up to 30 mm.) after smoking, and furthermore they find that this rise endures for 1 to 2 hours or even longer; if this is correct, habitual smokers maintain an abnormally high blood pressure during their waking hours. This extreme view is not accepted universally and Rolleston[79] quotes Dr. de Havilland Hall as insisting on the point that confirmed smokers tend to have a low blood pressure and also Sir Lauder Brunton as saying that in 19 out of 20 cases a systolic blood pressure of 100 mm. of mercury in a strong, healthy man without evidence of tuberculosis signified excessive smoking.

Whether, in the treatment of hypertension, a transient rise of 10 mm. of mercury or a tendency to a permanent lowering of blood pressure through tobacco smoking is to be interfered with by a medical advisor, it is difficult to say. Sir Clifford Allbutt's[77] statement in one of his last publications is worth considering: "I find no later evidence to weaken my opinion that the effect of tobacco in causing hyperpiesis or senile atheroma, if any, is negligible."

There are other matters in regard to the tobacco habit which, though they may bear no direct relation to blood pressure, still merit serious consideration in the treatment of hypertensive patients. The toxic effects of smoking manifest themselves in some persons much more readily than in others, and this individual susceptibility has to be taken into account in regulating this habit in patients. The action of tobacco in bringing about serious disturbances in cardiac rhythm (Neuhof[81]) and a form of angina pectoris (Moschcowitz[82]) is of frequent occurrence. The sensitive smoker often shows a series of symptoms that are undesirable in a patient whose cardiac action should be at its best to cope with a high arterial pressure. Nervous depression, cold and moist feet and hands, tachycardia, cyanosis, dyspnea on exertion, fatiguability and general inefficiency characterize this state. These individuals often show a lowered blood pressure, according to Hall and Lauder Brunton, as already noted, and according to more recent observations on heavy cigarette smokers by Ismail[74], but this hypotension is paid for in the coin of diminished muscular efficiency of the heart and arteries, and probably a depression of all the bodily functions, thus rendering it of doubtful value as a form of treatment. The observation of Crampton[83] that a transient effect of an excessive tobacco indulgence results in the picture of "blood ptosis" bears out the above statement.

Bibliography

1. Tixier, L.: Les variations normales et anormales de la tension artérielle humerale au cours de mensurations prolongées, Arch. d. Mal du Cœur, **12**: 337, 1919.
2. Gumprecht: Experimentelle und klinische Prüfung de Riva-Rocci-schen Sphygmomanometers, Ztschr. f. klin. Med., **39**: 377, 1900.
3. O'Hare, J. P.: Vascular reactions in vascular hypertension, Am. Jour. Med. Sc., **159**: 369, 1920.

4. Mosenthal, H. O. and Short, J. J.: The spontaneous variability of blood pressure and the effects of that upon high blood pressure, with special reference to sodium chloride, Am. Jour. Med. Sc., **165**: 531, 1923.
5. Maloney, W. J. M. and Sorapure, V. E.: The relief of states of high vascular, muscular and mental tension, N. Y. Med. Jour., **99**: 1021, 1914.
6. Grossman, M.: High blood pressure treatment by means of muscular relaxation, N. Y. Med. Jour., **102**: 645, 1915.
7. Diehl, H. S. and Sutherland, K. H.: Systolic blood pressure in young men including a special study of those with hypertension, Arch. Int. Med., **36**: 151, 1925.
8. Mosenthal, H. O.: The treatment of essential hypertension, Jour. Am. Med. Assoc., **91**: 698, 1928.
9. Addis, T.: Blood pressure and pulse rate levels under basal and daytime conditions, Arch. Int. Med., **29**: 539, 1922.
10. Blume, P.: Blood pressure during sleep, Jour. Am. Med. Assoc., **79**: 2046, 1922.
11. Dawson, B. F.: Discussion on hyperpiesis, Proc. Roy. Soc. Med., **43**: 1925–26.
12. Brooks, H. and Carroll, J. H.: A clinical study of the effects of sleep and rest on blood pressure, Arch. Int. Med., **10**: 97, 1912.
13. Campbell, H. E. and Blankenhorn, M. A.: Effect of sleep on normal and high blood pressure, Am. Heart Jour., **1**: 151, 1925.
14. MacWilliam, J. A.: Some applications of physiology to medicine, blood pressure and heart action in sleep and dreams; their relations to hemorrhages, angina and sudden death, Brit. Med. Jour., **2**: 1196, 1923.
15. Krumbhaar, E. B. and Crowell, C.: Spontaneous rupture of the heart, clinicopathologic study based on 22 unpublished cases and 632 from literature, Am. Jour. Med. Sc., **170**: 828, 1925.
16. Katsch, G. and Pansdorf, H.: Die Schlafbewegung des Blutdrucks, München. med. Wchnschr., **69**: 1715, 1922.
17. Wiggers, C. J.: Circulation in Health and Disease, Lea & Febiger, Philadelphia, 1923.
18. Meakins, J.: Arterial hypertension and hypotension and their clinical significance, Physiol. Rev., **7**: 431, 1927.
19. Herrick, W. W.: Hypertension and hyperglycemia, Jour. Am. Med. Assoc., **81**: 1942, 1923.
20. Symonds, B.: The blood pressure of healthy men and women, Jour. Am. Med. Assoc., **80**: 232, 1923.

21. Huber, E. G.: Systolic blood pressure of healthy adults in relation to body weight, Jour. Am. Med. Assoc., **88**: 1554, 1927.
22. Siler, J. F.: Review of the 1924 annual physical examination of officers on duty in the Philippine islands, Mil. Surgeon, **56**: 745, 1925.
23. Army Med. Bull., **8**: 225, 1923.
24. Dunham, G. C.: Variation in blood pressure as associated with variation in age and body weight, Internat. Clin., **3**: 81, 1925.
25. Fisk, E. L.: The relationship of high blood pressure to other impairments, Am. Med., **18**: 446, 1923.
26. Aubertin, C. and Coursier, L.: Obésité et hypertension, Presse Méd., **30**: 721, 1922.
27. Terry, A. H., Jr.: Obesity and hypertension, Jour. Am. Med. Assoc., **81**: 1283, 1923.
28. Rose, R. H.: The treatment of hypertension, Med. Jour. and Rec., **124**: 704, 1926.
29. Allen, F. M. and Sherrill, J. W.: Treatment of arterial hypertension, Jour. Metab. Research, **2**: 429, 1922.
30. Fahr, G. E.: Hypertension heart, Am. Jour. Med. Sc., **175**: 453, 1928.
31. Mosenthal, H. O.: Influence of protein food on increased blood pressure, Am. Jour. Med. Sc., **160**: 808, 1920.
32. Squier, T. L. and Newburgh, L. H.: Renal irritation in man from high protein diet, Arch. Int. Med., **28**: 1, 1921.
33. Strouse, S. and Kelman, S. R.: Protein feeding and high blood pressure, Arch. Int. Med., **31**: 151, 1923.
34. Lieb, C. W.: Effects of exclusive, long-continued meat diet, based on history, experiences and clinical survey of Vilhjalmur Stefansson, Arctic Explorer, Jour. Am. Med. Assoc., **87**: 25, 1926.
35. Thomas, W. A.: Health of a carnivorous race, Jour. Am. Med. Assoc., **88**: 1559, 1927.
36. Benedict, F. G. and others: Human vitality and efficiency under prolonged restricted diet, Publication 281, Carnegie Institution of Washington, 1919.
37. Mosenthal, H. O.: The relation of blood sugar to blood pressure, Am. Jour. Med. Sc., **176**: 761, 1928.
38. Wilder, R. M.: Hyperthyroidism, myxedema and diabetes, Arch. Int. Med., **38**: 736, 1926.
39. Neubauer, E.: Ueber Hyperglykämie bei Hochdrucknephritis und die Beziehungen zwischen Glykämie und Glykosurie beim Diabetes Mellitus, Biochem. Ztschr., **25**: 284, 1910.

40. O'Hare, J. P.: Glucose tolerance test in chronic vascular hypertension, Am. Jour. Med. Sc., **160**: 366, 1920.
41. Kylin, E.: Studien über das Hypertonie-Hyperglykämie-Hyperurikämiesyndrome, Zentralb. f. Inn. Med., **44**: 169, 1923.
42. Botti, A.: Lo zucchero del sangue negli arteriosclerotici ipertensivi, Policlinico (sez. prat.), **29**: 249, 1922.
43. Kramer, G. W.: Hypertension and diabetes, Am. Jour. Med. Sc., **176**: 23, 1928.
44. Miller, J. L. and Williams, J. L.: The effect on blood pressure and the non-protein-nitrogen in the blood of excessive fluid intake, Am. Jour. Med. Sc., **161**: 327, 1921.
45. Orr, J. B. and Innes, I.: Effect on arterial hypertension of increased fluid intake, Brit. Jour. Exp. Path., **3**: 61, 1922.
46. Engelen, P.: Blutdruckmessungen nach Biergenuss, Deutsche med. Wchnschr., **48**: 1130, 1922.
47. Dorner, G.: Ueber Beziehungen zwischen Blutdruck and Wasserzufuhr bei Nephritiden, Deutsch. Arch. f. klin. Med., **133**: 21, 1920.
48. Ambard, L. and Beaujard: Causes de l'hypertension arterielle, Arch. Gen. de Méd., **81**: 520, 1904.
49. Ambard, L.: L'origine renale de l'hypertension arterielle permanente, Sem. Méd., **26**: 361, 1906.
50. Loeb, A.: Ueber Blutdruck und Herzhypertrophie bei Nephritikern, Deutsch. Arch. f. klin. Med., **85**: 348, 1905.
51. Combe, A.: Beitrage zur Kenntnis der chlor-und stickstoffarmen Ernährung bei Morbus Brightii, Monatasschr. f. Kinderheilk, **4**: 13 and 82, 1905.
52. Munk, F.: Pathologie und Klinik der Nephrosen, Nephritiden und Schrumpfnieren, Berlin und Wien, 1918.
53. Bayer, R.: Ueber den Einfluss des Kochsalzes auf die Arteriosklerotisches Hypertonie, Arch. f. Exper. Path. u. Pharmakol., **57**: 162, 1907.
54. Lowenstein, C.: Ueber Beziehungen zwischen Kochsalzhaushalt und Blutdruck bei Nierenkranken, Arch. f. Exper. Path. u. Pharmakol., **57**: 137, 1907.
55. Allen, F. M.: Arterial hypertension, Jour. Am. Med. Assoc., **74**: 652, 1920.
56. Vogel, S. A.: Arterial hypertension and its treatment, New York State Jour. Med., **28**: 318, 1928.
57. Blaisdell, E. R.: Report of the results of treatment with salt-free diet in 33 cases of arterial hypertension, Boston Med. and Surg. Jour., **196**: 808, 1927.

58. Higley, H. A. and Field, C. W.: Some phases of blood chemistry of practical use to the practitioner, Med. Rec., **98**: 169, 1920.
59. Haughton, H. A.: The treatment of arterial hypertension with low sodium chloride dietary, Med. Rec., **101**: 441, 1922.
60. Konikow, M. J. and Smith, M.: The reduction of hypertension in an unusually difficult case by means of a "salt-free diet", Boston Med. and Surg. Jour., **185**: 281, 1921.
61. Musser, J. H.: Treatment of arterial hypertension, New York Med. Jour., **112**: 570, 1920.
62. Stone, C. T.: The treatment of essential hypertension, Texas State Jour. Med., **17**: 475, 1922.
63. Christian, H. A.: The relation that exists between hypertension, myocarditis and nephritis, Wisconsin Med. Jour., **20**: 455, 1922.
64. McLester, J. S.: The influence of rigid salt restriction in chronic nephritis, Proc. Am. Soc. for Clin. Invest., 6, 1921.
65. O'Hare, J. P.: Discussion of paper of McLester, Proc. Am. Soc. for Clin. Invest., 1921.
66. Strouse, S.: Dietetic therapeutics. Case I, hypertension, the effect of high protein and high salt intake, Med. Clin. North America, **5**: 229, 1921.
67. Mosenthal, H. O.: Renal function as measured by the elimination of fluids, salt and nitrogen, and the specific gravity of the urine, Arch. Int. Med., **16**: 733, 1915.
68. Hartwick, A. and May, G.: Blutmengenbestimmungen mittels der Farbstoffmethode, Ztschr. f. d. Gesamte Exp. Medizin, **53**: 677, 1927.
69. Saule, H. D., Buchanan, T. E. and Darrow, D. C.: Blood volume in fever, Jour. Clin. Invest., **5**: 229, 1928.
70. Alvaraz, W. C., McCalla, R. L. and Zimmerman, A.: Hypertension and constipation, statistical inquiry, Arch. Int. Med., **38**: 158, 1926.
71. Allbutt, C.: Diseases of the Arteries, MacMillan Co., London, 1915.
72. Cadbury, W. W.: The blood pressure of normal Cantonese students, Arch. Int. Med., **30**: 362, 1922.
73. Foster, J. H.: Blood pressure of foreigners in China, Arch. Int. Med., **40**: 38, 1927.
74. Ismail, A.: Etiology of hyperpiesis in Egyptians, Lancet, **2**: 275, 1928.
75. Roddis, L. H. and Cooper, G. W.: The effect of climate on blood pressure, Jour. Am. Med. Assoc., **87**: 2053, 1926.
76. Huber, E. G.: Systolic blood pressures of healthy adults in relation to body weight, Jour. Am. Med. Assoc., **88**: 1554, 1927.

77. Allbutt, C.: Arteriosclerosis, MacMillan Co., London, 1925.
78. Lee, W. E.: Action of tobacco smoke with special reference to arterial pressure and degeneration, Quart. Jour. Exp. Physiol., **1**: 335, 1908.
79. Rolleston, H.: Medical aspects of tobacco, Lancet., **1**: 961, 1926.
80. Cook, H. W. and Briggs, J. H.: Clinical observations on blood pressure, Johns Hopkins Hosp. Reports, **11**: 451, 1903.
81. Neuhof, S.: Sino-auricular block due to tobacco poisoning, Arch. Int. Med., **17**: 659, 1916.
82. Moschcowitz, E.: Tobacco angina pectoris, Jour. Am. Med. Assoc., **90**: 733, 1928.
83. Crampton, C. W.: Gravity resisting ability of the circulation, Am. Jour. Med. Sc., **160**: 721, 1920.

CHAPTER VIII

TYPES OF INCREASED BLOOD PRESSURE

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Physiological Classification of Hypertension

Essential hypertension, the "hyperpiesis" of Sir Clifford Allbutt, the "hypertensive cardiovascular disease" of Theodore Janeway, is a disease of unknown etiology, characterized by a persistent and progressive rise of both the systolic and the diastolic blood pressure.

Up to the present time it has been usual to regard every person with a blood pressure above the average normal as "hypertensive" and affected with the malady, essential hypertension. This probably is not correct. There are a number of forms of hypertension differing greatly from one another, and it

would be very misleading in many ways to consider them all in the same category. An attempt was made in Chapters I and II to analyze some of the facts bearing on this question. A number of them, at the risk of repetition, will be taken up in this chapter. The main object of this presentation is to attempt a differentiation between various types of elevated blood pressure so that those which are harmless, or comparatively so, may be distinguished from those that entail serious consequences. An effort of this sort necessarily must be incomplete and faulty because it represents only a step in the long road leading to a final analysis of the situation.

Constitutional Hypertension

Each human being has a blood pressure characteristic of his or her personality and physical build. Such blood pressures may be so at variance with the accepted averages that they are considered as examples of low or high blood pressure. It is often said that any person with a systolic arterial pressure above 140 mm. or 150 mm. is a "hypertensive". This is correct in so far that we may regard these readings as signifying an arterial tension above the normal average, but must not be stretched to imply that these patients are, or will soon be, suffering from essential hypertension, a condition in which the blood pressure rises to such heights as to threaten life through secondary lesions in the heart or arteries. Examples of such constitutional, non-progressive high blood pressures have been given in Tables 10 and 11 in Chapter II. There is no known way of differentiating these cases from the advancing type of hypertension, except by observation over a period of six to twelve months. These individuals, because the strain on their arterial and cardiac systems is greater than where a normal or

low blood pressure exists, are supposed to have a correspondingly less favorable mortality rate. However, in spite of their slight physical limitations, they carry on very well.

Cases Grouped According to the Elevation of Systolic or Diastolic Pressure or Both

The relations that may exist between systolic and diastolic blood pressures are given in Table 29. Such a classification of

Blood Pressure		Remarks
Systolic	Diastolic	
230	92	Group 1. — Examples of comparatively low diastolic pressure and markedly increased systolic pressure.
184	90	
220	98	
180	95	
225	94	
200	96	
234	134	Group 2. — Examples of simultaneous increase of systolic and diastolic blood pressure.
232	132	
200	130	
245	140	
280	136	
230	135	
170	120	Group 3. — Examples of increased diastolic pressure with a comparatively slight rise in systolic tension; these cases are comparatively rare.
177	120	
161	120	
190	130	
170	110	

TABLE 29. — Showing the various relations that may exist between systolic and diastolic blood pressures.

hypertensive conditions has been suggested lately by Foster[1], by Frost[2] and by Mosenthal[3]. The various interpretations which may be accorded the systolic blood pressure on the one hand, and the diastolic on the other, make it evident that it is important to make this classification.

Until recently it has been accepted generally that hypertension is brought about by an increase in the peripheral resistance which is overcome by a compensatory rise in blood pressure. In the researches of Boas and Frant[4] it is shown that in most instances of hypertension the capillary pressure remains normal, indicating that the peripheral resistance is adjusted so that the capillary flow and blood supply are unchanged. The question as to which is cause and which effect, whether raised peripheral resistance or increased arterial pressure is primary, is not clear, and yet it is of the greatest importance. Boas[5] has shown that the so-called "capillary pulse" is not a manifestation of the capillaries, but is due to an exaggerated pulsation of the arterioles; the observations of Krogh[6], Richards[7], and Cobb and Talbott[8] demonstrate that the amount of blood flowing in the capillaries of voluntary muscles, kidneys, heart muscle, brain and presumably all tissues, is directly proportional to their activity. In other words, the arterioles act as "stop-cocks" that control the flow of blood to the capillaries; their function is to draw upon the potential energy of arterial pressure and convert it into blood flow, supplying the capillaries as demand arises. Such a physiological conception applied to the disease essential hypertension makes the increased blood pressure the primary factor and the constriction of the arterioles a compensatory effect. There are certain exceptions to this statement that will be taken up a little further on. Essential hypertension, therefore, should be considered as a general functional disturbance, brought on by an increased tonicity of the arteries between the heart and the arterioles.

Excluding blood viscosity and blood volume, which have been shown to have little or no practical bearing in clinical medicine as far as the usual case of hypertension is concerned,

there remain three factors that may bring about an increase of blood pressure; these are the cardiac output or pulse volume, the peripheral resistance and the increased tonicity of the arteries.

Before analyzing the influence of these factors upon blood pressure and the bearing they have upon the treatment of hypertension, it is very necessary to call attention to the enormous power of the body to regulate and compensate for changes

Date	Blood Pressure		Pulse
	Systolic	Diastolic	
1926, Dec. 9	208	128	70
1927, Jan. 6	156	108	72
Feb. 9	210	135	72
Mar. 23	164	128	72
Apr. 20	152	110	72
June 16	204	122	84
July 21	167	106	72

TABLE 30. — Mrs. A. M., aged 41; note how the blood pressure varies while the pulse rate remains constant. An example of fluctuations of blood pressure brought about by variations in the peripheral resistance (patient is subject to asthma and paroxysmal dyspnea) and in the tonicity of the arteries, while the third factor, concerned in the production of blood pressure, the cardiac output, persists unchanged.

in one or another part of the circulation. The experiments of Anrep and Starling, Table 2 (Chapter I), demonstrate very beautifully that extensive reflex adjustments of blood pressure may come about, and show also how delicate a matter is speculation regarding the effect of any given cause upon arterial tension. Clinically, marked variations of blood pressure, in spite of a constant pulse rate, are often noted; in fact this may be considered to be a rule rather than an exception (see Table 30; also Table 3, Chapter I).

Group 1, Increased Systolic and Low Diastolic Blood Pressure. — This change in arterial tension is caused by a large

pulse volume or by a general rigidity of the arterial wall. In heartblock with its very low pulse rate, and in aortic insufficiency and hyperthyroidism, the great amount of blood expelled with each cardiac contraction influences the pressure so that there is a tendency for the systolic pressure to increase, while the diastolic remains comparatively low. In one of Read's[9] cases the pulse rate was as low as 28 and the manometer reading as high as 240/100. It is easy to understand, from a mechanical viewpoint, how an increased resistance in the arterial tree, that is, loss of elasticity, presenting an unyielding opposition to the advancing blood wave, would increase the systolic pressure and allow the diastolic values to remain normal. Such instances of more or less universal arteriosclerosis undoubtedly do occur and may be responsible for many of the changes in blood pressure, especially in older people. (Tables 8 and 9, Chapter II). In fact, Frost[2] notes that in average normal readings the systolic pressure increases twice as fast as the diastolic with advancing years. It is probable that arteriosclerosis and consequent arterial rigidity, characteristic of old age, are responsible for such a change. Cases with a high systolic and approximately normal diastolic blood pressure must, in the first place, be investigated as instances of increased cardiac output (heartblock, aortic insufficiency, hyperthyroidism most commonly) and must be considered furthermore as having a generalized arteriosclerosis. Patients, whose diastolic pressure is low, do comparatively well no matter what level the systolic tension reaches. As one text book has put it, "the diastolic pressure represents the constant blood pressure" and consequently the persistent strain to which heart and arteries are subjected, while the systolic level is maintained only during a fraction of the cardiac cycle. The majority of these cases probably are

not true examples of essential hypertension, which is characterized by a high diastolic as well as systolic pressure; however, complications in the heart, basal metabolism or arteries may render the diastolic reading comparatively low in essential hypertension. These cases should be investigated always for the conditions mentioned above (increased cardiac output, widespread arteriosclerosis) before the diagnosis of essential hypertension is accepted even tentatively.

Group 2, Elevated Systolic as well as Diastolic Pressure. —This may be brought about in two ways: In the first place, the primary change may be a contraction of the smooth musculature of the arterioles, resulting in an increase of the peripheral resistance with a compensatory sequel of an augmented tonicity of the larger arteries so as to maintain an adequate blood flow in the capillaries; in the second place, and this is the more usual course of events and represents the state of affairs in the disease essential hypertension, the process is reversed, and the stimulation of the tone of the larger arteries appears to be the primary disturbance, followed by the stop-cock action of the arterioles, allowing only a proper amount of blood to flow to the capillaries.

A primary increase in peripheral resistance heretofore has been regarded generally as the cause of hypertension. When cases of hyperpiesis are studied, the findings in a few of these are evidently in accord with this idea. They exhibit very definite intermittent signs of spasm in the smooth musculature of the finer arteries, notably asthma, paroxysmal dyspnea and blanching of one or another of the fingers or toes; furthermore, the blood pressure in these patients is prone to be extremely variable. This is only to be expected if the hypertension brought on by increased arterial tone is a compensating measure

for the peripheral vasoconstriction which distinctly occurs only at intervals. Such cases are not very common; one of the most marked blood pressure changes in an instance of this sort is illustrated in a case carefully observed by Dr. I. W. Kingsbury of Hartford, Conn. I am indebted to Dr. Kingsbury for the data presented (see Table 31).

Date	Blood Pressure		Date	Blood Pressure	
	Systolic	Diastolic		Systolic	Diastolic
1923, Sept. 29	230	120	1925, Jan. 12	120	80
Oct. 10	230	120	26	130	80
26	195	125	Feb. 25	180	100
Dec. 3	150	95	Mar. 19	80	60
1924, Feb. 7	120	80	Apr. 6	135	95
Apr. 26	130	90	May 11	130	85
June 27	250	140	June 20	150	100
July 11	195	115	Aug. 7	160	80
28	115	70	Sept. 9	190	120
Sept. 10	195	90	26	210	110
Oct. 2	115	79	Oct. 3	230	120
17	115	75	7	210	135
Nov. 17	180	110	13	235	135
Dec. 3	120	80			

TABLE 31. — Mrs. X, age 64; subject to sudden fainting spells, has "dead fingers" and "dead toes" at frequent intervals, periodic looseness of the bowels without cause and several attacks of blurred vision; all these facts point to an intermittent peripheral vasoconstriction. This is apparently the cause for the variable blood pressure found in this case. (Data from Dr. I. W. Kingsbury.)

A very interesting instance of intermittent peripheral vasoconstriction has been reported by Dr. C. H. Mayo[10]. This patient suffered for one and a half years with sudden attacks of precordial discomfort, occipital headache, general pallor, cold and clammy skin and choking sensations followed by nausea and vomiting; the attacks lasted from $\frac{1}{2}$ to 2 to 3 hours; they came on every day, or at longer intervals, sometimes only every 3 days; during the attack the blood pressure rose from

120–130 systolic and 80 diastolic to 280–320 systolic and 160–180 diastolic. A blastoma, of yellow color suggesting ganglion cells, was removed from the retroperitoneal tissue behind the tail of the pancreas. Post operatively the blood pressure was not above 120, and the patient was much improved.

Another important case report of this sort is that of Oppenheimer and Fishberg[11]. This patient was subject to intermittent exacerbations of an existing hypertension apparently brought on by vasoconstriction of the cerebral vessels. Accompanying the successive blood pressure elevations there were convulsions, which subsided as the arterial tension diminished. These authors give a splendid, constructive review of the literature to show that the so-called uremic symptoms, commonly accredited to toxic irritation of the central nervous system (such as epileptiform convulsions, coma, headache, amaurosis, hemiplegia and aphasia), are in reality due to cerebral anemia induced by vasoconstriction.

Besides the intermittent and marked elevations of blood pressure, described above, more permanent ones sometimes occur. These may be moderate in degree and entail no immediate consequences, but this is not so in every instance. One case particularly is noteworthy in this connection, that of a boy 12 years old (Table 32) who had had a blood pressure slightly above the normal, an accompaniment of a chronic nephritis. For no apparent reason the blood pressure, especially the diastolic, rose, reaching astounding figures, and death occurred as the result of exhausting convulsions. It may be of interest to add that a decapsulation of the kidney did not lower the blood pressure. This operation was performed on the theory that partial closure of the glomerular arterioles and capillaries might be the cause of the hypertension and that kidney decapsulation

could, by lifting the pressure on the glomerular vessels, restore the circulation to normal.

	Blood Pressure		Blood Urea N mg. per 100 c.c.	Remarks
	Systolic	Diastolic		
1920, March				Pneumonia, mastoid operation, followed by albuminuria and edema.
1922, March	112	84	9.0	
1923, Jan.	114	82	15.0	
Feb.	146	110		
1924, Jan.	139	112	18.0	
Apr.	188	152	20.0	
	250	210		
	212	154	33.0	
May	202	162	28.0	Kidney decapsulation.
	218	164	32.0	Died.

TABLE 32. — Boy, aged 12; a sharp rise of blood pressure for no apparent reason in a case of chronic nephritis; presumably, there was marked peripheral constriction especially of the cerebral arterioles as there were repeated general convulsions to which the patient finally succumbed; the very high diastolic pressure is worth noting.

The last two cases really represent an intermittent peripheral vasoconstriction, in both instances affecting the cerebral blood vessels, superimposed upon a more or less constantly elevated blood pressure, that is, an essential hypertension. Possibly it is not surprising that the vasomotor control should run riot at times, when the blood pressure is extremely high and compensatory efforts to maintain a normal circulatory flow are strained to the utmost. These two patients illustrate the occurrence of excessive local peripheral vasoconstriction in persons afflicted with an essential hypertension, that is, a permanently elevated systolic and diastolic pressure, brought about by a primary increase in arterial tone.

The usual case of hypertension does not present these

marked signs of peripheral vasospasm; the blood pressure, while fluctuations do occur, does not exhibit such very wide and sudden variations. The increased tone of the arteries lying between the heart and the arterioles apparently cause the hypertension, and the contraction of the arterioles is a secondary phenomenon which the body initiates as a reflex compensatory act to regulate the flow of blood to the capillaries, thus adjusting itself to the change in the arterial pressure. The evidence for this theory has been taken up in a previous section. Some endocrine or toxic factor is the most probable cause for the rise in vascular tone; many very suggestive researches have shown that heredity plays an important rôle; the hypertension of acute nephritis, at least, would appear to fall in the same category, as Kylin[12] and others have demonstrated definitely that the increased blood pressure precedes the signs of kidney involvement by an appreciable interval.

Cases of the diseased condition commonly spoken of as primary or essential hypertension really constitute this group. Clinically, this disturbance in vasomotor control is characterized by a high systolic as well as a high diastolic pressure, by a tendency to progress over a period of months (see Table 12, Chapter II) and to result, through mechanical stress, in changes in the heart and arteries, especially those of the brain and kidneys, these changes being the usual cause of death.

A differentiation between these two subdivisions (the one with primary peripheral vasoconstriction, the other with primary increased arterial tone) of the second group of hypertensive cases furnishes a clue as regards the use of vasodilators that have been so much discussed in this connection. The nitrites dilate the peripheral vessels, bringing about a flushed, congested, uncomfortable sensation when used in effective

dosage. This is extremely desirable as an emergency measure in paroxysmal constriction of the peripheral vessels, but is obviously contraindicated in the usual type of hypertension where the primary fault lies in the overstimulation of the vasomotor tone of the larger arteries.

Group 3, Comparatively Low Systolic and High Diastolic Pressure. — Finally, the third group of hypertensives, with a comparatively low systolic and high diastolic pressure, remains to be considered. In my experience these cases are not common; Frost[2] found only 3.9 per cent. of his subjects to be in this category; it is most probable that such patients are the victims of insufficient cardiac action, and this phase of their condition demands attention before further steps are taken.

Summarizing the statements made up to this point, the following may be noted: There are three groups of hypertensive cases, fairly clearly distinguished from one another, and only one is to be regarded in the category of essential hypertension.

Group 1. High systolic, comparatively low diastolic pressure, associated with increased cardiac output (heartblock, aortic insufficiency, hyperthyroidism, etc.,) and loss of arterial elasticity (generalized arteriosclerosis). To a greater or less degree, the latter factor plays a part in all older individuals.

Group 2. High systolic and high diastolic pressure; these cases fall into two, possibly three, sub-groups:

(*a*) Primary, increased peripheral vasoconstriction; such cases are comparatively rare.

(*b*) Primary increase of tone in arteries between the heart and arterioles with secondary compensatory constriction of the arterioles; these are the cases known clinically as essential hypertension.

(*c*) There are certain patients who combine (*a*) and (*b*); that

is, they may exhibit a true essential hypertension, and at times have peripheral vasoconstriction besides, producing symptoms such as paroxysmal dyspnea, convulsions, etc.

Group 3. Comparatively low systolic and high diastolic pressure, with a low pulse pressure; such cases are not common and are usually associated with myocardial insufficiency. The changes of group 3 are often superadded to the blood pressure of group 2, especially in the cases of essential hypertension where the cardiac muscle becomes relatively insufficient.

Classification of Essential Hypertension

The expression "high blood pressure" conjures up in the minds of physicians, as well as of the laity, a picture of the serious heart, brain or kidney conditions that often accompany or follow it. In the foregoing paragraphs an attempt has been made to differentiate various types of hypertension and to show that many of these do not have the serious outlook of the disease generally known today as essential hypertension.

Since Richard Bright published his work nearly a century ago, it has been known that cardiac hypertrophy (and, as we now interpret it, elevated blood pressure) is found in many cases of inflammatory and degenerative diseases of the kidney. Largely due to the effort of Sir Clifford Allbutt, it became known how hypertension might occur independently, not only of the kidney, but of any anatomical impairment throughout the body. From the nomenclature applied simultaneously by others to this disturbed functional state, it is evident that they had the same idea in mind. It was termed "hyperpiesis" by Sir Clifford Allbutt, "presclerosis" by Huchard, "pre-albuminuric stage of Bright's disease" by Mahomed and "hypertensive cardiovascular disease" by Theodore Janeway. All these

names indicate that the relation of blood pressure elevation and kidney pathology was no longer regarded as one of invariable cause and effect. With the advent of successful tests for renal function, about 15 years ago, it became evident that in the majority of instances of increased arterial pressure the kidneys show little, if any, impairment. Yet in Germany there are still many who believe that an elevated blood pressure is always the signal of kidney changes. Such men as Romberg, Volhard and Fahr champion this idea, but even in Germany the contrary minded, Löhlein, Kylin, Munk, von Monakow and others, are making themselves heard. Not only do many cases of hypertension show no clinical evidence of kidney disease, but there is also the outstanding fact to be considered that practically all pathologists with a wide autopsy experience have come in contact with one or more instances of markedly elevated arterial tension during life and normal kidneys at the post mortem examination. Even Fahr, with the very thorough histological examinations at his command, has had this experience. Bright's disease is, as a rule, accompanied by hypertension, but unless we deliberately close our eyes to the existing facts, we must recognize that, in the first place, under clinical observation, most cases of hypertension show little or no impairment of renal function, and, in the second place, that in these cases the kidney may be completely free from anatomical lesions or show changes which may very well be secondary to the mechanical strain of the increased blood pressure. A great deal more might be said on this subject, but lack of space prevents a fuller discussion of this interesting and much debated question.

The "hyperpiesis" of Sir Clifford Allbutt has been pretty generally supplanted by the name "essential hypertension" in this country. The objection to the qualifying word, "essential",

on the ground that it has no significance, becomes void when it is acknowledged that the cause of the high blood pressure is unknown. Essential hypertension may be defined as a disease characterized by a high systolic as well as an elevated diastolic pressure, both of which have a tendency to rise over a period of months and years, and which bring about secondary changes in the heart and the arteries of the brain and kidneys, that are a common cause of death. The varieties of hypertension may be classified in two ways: first, on an anatomical basis, according to the location of the predominant secondary changes, and, second, according to the character of the secondary changes, into "benign" and "malignant," or "mild" and "severe" types.

Anatomical Classification of Essential Hypertension

This is determined according to the predominant lesions brought about by the mechanical strain caused by the increased blood pressure. A study of more than 400 autopsies on cases of primary (essential) hypertension by Bell and Clawson[13] yielded the following grouping, according to causes of death:

Cardiac Group	60 per cent.
myocardial insufficiency	44 per cent.
coronary disease	16 per cent.
Cerebral Group	19 per cent.
Kidney Group	9 per cent.
Miscellaneous Group	12 per cent.

These findings agree approximately with those arrived at by Theodore Janeway in a clinical survey made in 1913 and with all extensive statistical studies of this disease. Thus, we are justified in grouping cases of essential hypertension into cardiac, cerebral and renal classes. These may be remembered as

comprising roughly 60, 20 and 10 per cent, of the cases, respectively. It is important to bear these facts in mind, since much may be accomplished by prophylactic therapy, especially for the heart. A fuller description of the changes occurring in the heart, brain and kidneys will be given in the next chapter.

Classification of Essential Hypertension According to the Severity of the Secondary Lesions

The division of cases of essential hypertension into benign and malignant groups has been made on at least three different bases. Since these terms are now widely and often somewhat carelessly employed, it may be worth while to define them according to the conceptions of various clinicians and pathologists.

Volhard and Fahr[14] in 1914 called those cases of hypertension benign where, in spite of the almost inevitable vascular sclerosis of the kidney, renal function was not diminished. The cases where kidney activity was extensively impaired through a progressively obliterative arteriolosclerosis, they called malignant. The division of hypertensive conditions into benign and malignant on this basis has been practically given up.

Fahr[15] more recently has made the distinction between benign and malignant nephrosclerosis; the former shows only arteriosclerotic changes, while the latter exhibits also inflammatory lesions, especially in the afferent glomerular arteries. (For a thorough and interesting discussion of this intricate subject see Fahr[15].) Bell and Clawson[13] describe a certain acute, fulminating form of hypertension terminating in uremia. In such kidneys the arterioles were largely necrotic and partially or completely occluded. Usually there was necrosis only; in occasional instances inflammation was present. Pathologically,

this absence of signs of inflammation differentiates these cases from those of Fahr's malignant nephrosclerosis. The important point to note is the fact that acute renal insufficiency and uremia may develop in patients with high blood pressure. Dr. Paul Klemperer, pathologist of Mt. Sinai Hospital in New York, has records of about 20 autopsies of this sort showing an acute necrotizing arteriolosclerosis, which had developed rapidly in patients with a very high systolic and diastolic blood pressure of long duration.

Very recently Keith, Wagener and Kernohan[16] again have called attention to malignant hypertension. This they describe as a clinical state characterized by a typical retinitis associated with marked hypertension and adequate renal function. Apparently, most of these patients die of cerebral complications. Consequently they might be classified in the cerebral group, on anatomical grounds. These cases nearly all had a very high diastolic blood pressure ranging from 140 to 190.

Taking all these facts into consideration, it would seem logical to classify essential hypertension as benign or malignant, no matter whether the termination is through cardiac, cerebral or renal disease. Better terms than "benign" and "malignant" might be "mild" and "progressive" or "severe". Furthermore, every patient with a diastolic blood pressure persisting at a level of 130 or higher should be regarded as an example of severe essential hypertension and the prognosis as exceedingly grave.

Bibliography

1. Foster, N. B.: Treatment of hypertension, Jour. Am. Med. Assoc., **79**: 1089, 1922.
2. Frost, H. M.: Hypertension and longevity, Life Insurance Medicine, **1**: 178, 1926. Published by New England Mutual Life Ins. Co., Boston.

3. Mosenthal, H. O.: The treatment of high blood pressure, Med. Clin. North America, **5**: 1139, 1922.
4. Boas, E. P. and Frant, S.: The capillary blood pressure in arterial hypertension, Arch. Int. Med., **30**: 40, 1922.
5. Boas, E. P.: Nature of so-called capillary pulse, Arch. Int. Med., **29**: 763, 1922.
6. Krogh, A.: The Anatomy and Physiology of Capillaries, Yale University Press, 1924.
7. Richards, A. N.: Nature and mode of regulation of glomerular function, Am. Jour. Med. Sc., **170**: 781, 1925.
8. Cobb, S. and Talbott, J. H.: Studies in cerebral circulation. A quantitative study of cerebral capillaries, Tr. Assoc. Am. Physicians, **42**: 255, 1927.
9. Read, J. M.: Pulse pressure, its probable relationship to stroke volume, Proc. Soc. Exper. Biol. and Med., **24**: 564, 1927.
10. Mayo, C. H.: Paroxysmal hypertension with tumor of retroperitoneal nerve, Jour. Am. Med. Assoc., **89**: 1047, 1927.
11. Oppenheimer, B. S. and Fishberg, A. M.: Hypertensive encephalopathy, Arch. Int. Med., **41**: 264, 1928.
12. Kylin, E.: Die Hypertoniekrankheiten. J. Springer, Berlin, 1926.
13. Bell, E. T. and Clawson, B. J.: Primary (essential) hypertension: a study of four hundred and twenty cases, Arch. Path., **5**: 939, 1928.
14. Volhard, F. and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, 1914.
15. Fahr, T.: Handbuch d. Speziellen Pathologischen Anatomie und Histologie (Henke und Lubarsch), **6**: 368, J. Springer, Berlin, 1925.
16. Keith, N. M., Wagener, H. P. and Kernohan, J. W.: The syndrome of malignant hypertension, Arch. Int. Med., **41**: 141, 1928.

CHAPTER IX

ESSENTIAL HYPERTENSION

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Definition

Essential hypertension is a functional disorder, the cause of which is unknown, characterized by a progressively increasing elevation of both systolic and diastolic blood pressure; the mechanical strain of the high arterial tension produces changes in the heart and in the arteries, especially those of the heart, the brain and the kidneys, often with a fatal result.

For the reasons discussed in Chapter VIII, there should not be included under the caption, essential hypertension, those cases in which the blood pressure is elevated intermittently, those in which there is a rise of the systolic pressure only and not of the diastolic, and finally those in which the blood pressure values do not rise progressively to a considerable height, at least 180, systolic, and 110, diastolic. Some of these cases may be potentially instances of essential hypertension; clinically they are not, as they are not subject to the secondary anatomical changes given as part of the definition and under these cir-

cumstances are not in need of medical supervision. They constitute the type of hypertensive patient that does well without a doctor's care, whereas the true case of essential hypertension will live longer and more comfortably under medical supervision.

Etiology

The direct cause of essential hypertension has not been discovered. We may ascribe to an increase in arterial tone, peripheral resistance and cardiac power the responsibility for a permanent elevation of systolic and diastolic pressure, yet these factors are but the result of some primary disturbance, possibly in the endocrine system, and thus far we have not approached even remotely a solution of this problem.

Incidence

A blood pressure distinctly higher than the average normal is present in about 1.6 per cent. of the younger adult population; Frost[1] found 1.74 per cent. and Knight[2], 1.6 per cent. in candidates for life insurance; Diehl and Sutherland[3], demonstrated a persistent elevation of systolic pressure above 140 mm. of mercury in 1.6 per cent. of the male college students at the University of Minnesota. With more advanced years the incidence undoubtedly is higher.

There are no mortality statistics available in regard to essential hypertension, as these deaths are ascribed to various forms of cardiac or kidney disease or to apoplexy, but not heretofore to essential hypertension. Fahr[4] calculates "for the registration area of the United States for 1924 that approximately 140,000 deaths in persons fifty years of age and older are due to hyperpiesia, wholly or in part. This is as great as the

combined death rates for cancer, all forms of tuberculosis and all forms of respiratory disease including pneumonia for the same age, category and year, and twice as great as the death rate for cancer." Fahr[4] believes this to be reckoned conservatively, and adds that the figure for deaths from essential hypertension, quoted above, "is 23 per cent. of all deaths in persons fifty years of age or older". Absolute accuracy, of course, cannot be claimed for these estimates; however, they serve to emphasize the conviction of many as to the wide prevalence of essential hypertension and its frequency as a cause of death, beyond that of any other disease, in persons over 50 years of age.

Age

It is universally conceded that essential hypertension usually begins between the ages of forty and fifty. It is occasionally met with in children; in fact, it may occur at any age.

Sex

Statistics are hopelessly confused in this regard since most reports on this subject erroneously include cases with a high systolic pressure and a normal diastolic. Such patients are not suffering with essential hypertension and should be classified separately. It may be that the hypertension in women after the menopause (Table 9 and discussion, Chapter II) falls in this category. Essential hypertension is common in both men and women, and it would be difficult to furnish an accurate estimate as to percentage occurrence, based on sex.

Heredity

There is a distinct tendency for essential hypertension to be transmitted from one generation to the next. Rosenbloom[5],

Wiseman[6], de Nador Nikititch[7], and O'Hare, Walker and Vickers[8] find this to be true. One of the most thorough studies of this matter is that of Weitz[9], who concludes that hypertension is a constitutional disease with a familial tendency, affecting women as well as men, and that in its inheritance it follows the Mendelian law and is a dominant characteristic. The fact that certain races, as the Chinese, are not subject to essential hypertension, while others, for instance the Egyptians, are prone to suffer from it, bears out this idea. We are not brought very much closer to a solution of the riddle as to the ultimate cause of hypertension, since it is absolutely unknown exactly what causative functional disturbance is inherited. However, it does eliminate certain factors such as infectious foci, alcohol, tobacco, etc., as causative agents of major importance.

For a discussion of the effects of *habits* and *daily routine* such as mode of life, physical exertion, weight, diet, climate, alcohol, tobacco, etc., reference is made to Chapter VII.

Arteriosclerosis of Cerebral Vessels

Arteriosclerosis of the cerebral vessels has been described by Bordley and Baker[10] as a cause for a permanently elevated blood pressure through interference with the blood supply to the vasomotor center in the medulla. Bordley and Baker[10] recognize the possibility that such changes in the blood vessels of the brain may be either primary or secondary to the hypertension, but there is no direct evidence on this point in their material. Cutler[11], recently, found no sclerosis of the arteries supplying the medulla and pons in more than half of eighteen cases of hypertension. He concludes: "If the high blood pressure is due to a lack of blood supply to the vasomotor center, it is evident from the studies that this abnormal condition is not

caused by any demonstrable anatomic changes in the arteries of this region."

Guanidin

Guanidin causes a prolonged rise of blood pressure in animals. Major[12] in an admirable series of experiments has demonstrated this conclusively; he also has found that "certain hypertensives show in their blood an increased amount of some substance giving the same color response as guanidin and having certain chemical properties like those exhibited by the guanidin bases". These results, thus far, have not been applied successfully to clinical medicine; it remains for future observations to make a final appraisal of the rôle guanidin may play in the production of essential hypertension in man.

Blood Chemistry

The former conception that the metabolites — urea, uric acid, creatinin — accumulating in the blood as the result of renal insufficiency, are responsible for an increase in blood pressure, has been definitely abandoned. There are countless observations disproving this. There is also no direct relation between sodium chloride and glucose in the blood and hypertension. (See Chapter VII). More recently the theory has been advanced that a calcium deficiency and an excèss of potassium bring about a rise in arterial pressure. Thus Reid[13] is inclined to believe that lack of food calcium is a cause for hypertension as well as rickets; Kylin[14], in a number of publications, shows lower blood calcium figures in cases of hypertension than in normal persons, but the difference is very slight. Stieglitz[15] was unable to demonstrate a significant hypocalcemia in the hypertension of pregnancy. Final judgment in regard to the

clinical relationship of hypertension to calcium and potassium must be withheld for the present.

Pathology

The outstanding problem in regard to the pathological lesions in essential hypertension is whether they are the cause of the rise in blood pressure, or whether they are brought about by the strain which a persistent elevation of arterial pressure entails; in other words, are the anatomical changes cause or effect, primary or secondary? Evidence for the belief that the prevalent kidney changes are a result of the increased blood pressure has been given in Chapter VIII under the topic of the classification of essential hypertension into mild and severe. (See also the excellent papers of Moschcowitz[16] on this subject.) One other pathological lesion that has been given etiological importance is that of a generalized arteriosclerosis. Through a stiffening of their walls and roughening and narrowing of the internal surfaces of arteries and arterioles, the peripheral resistance to the blood flow is increased, and a compensatory rise in blood pressure is supposed to follow. This theory is pictured and made vivid by the well-known description of generalized arterio-capillary fibrosis of Gull and Sutton[17]. However, as will be shown in the following paragraphs, neither the sclerosis of arteries nor of arterioles is generalized in hypertension; furthermore, sclerosis of the arterial tree causes a rise in systolic pressure only and cannot account for the increase in diastolic pressure so characteristic of essential hypertension. For these reasons the idea that essential hypertension is the result of arteriosclerosis has been abandoned. We believe, therefore, that all pathological changes related to essential hypertension are secondary to it, and they will, therefore, be described from this point of view.

Arteries. — We have to thank Sir Clifford Allbutt[18] for the division of arteriosclerosis into two main types, the decrescent, degenerative or senile arteriosclerosis and the lesions consequent upon a permanently increased blood pressure. There are other forms of arterial degeneration such as those characteristic of lues and of thromboangiitis obliterans, but these are not often confused with the arterial changes occurring in hypertensive states. Many authors consider a differentiation between the anatomical changes of the senile and hypertensive types of arteriosclerosis to be impossible while others believe that a difference exists both in the character and distribution of the lesions.

From the studies of Moschcowitz[19] on the pulmonary vessels, it would appear that arteriosclerosis in those arteries is due almost solely to an increased pressure within the lesser circulation. It is probable that the height of pressure within the arteries of the greater circulation, as well, plays a much greater rôle in the production of arteriosclerosis than has been supposed heretofore.

The main characteristic of the arterial lesion in hypertension, as distinguished from that of the decrescent type of arteriosclerosis, has been claimed to be the marked hypertrophy of the muscular, elastic and connective tissues. The occurrence of changes in the smooth muscle have been stressed especially. Pal[20], believing that the increased tone of the arteries plays a part in the production of essential hypertension, subscribes to this view. Moschcowitz[21] finds that in transient cases of hypertension the radial arteries become thickened because of such a muscular hypertrophy, which disappears after the blood pressure has returned to a normal level for a few weeks.

The distribution of sclerotic arterial lesions in essential

hypertension and their clinical importance is as follows: The ascending *aorta* in cases of long duration becomes lengthened and dilated; sclerotic changes have been described in both the ascending and descending portions of the aorta; the process is of importance, as it may involve the aortic valves, resulting in aortic insufficiency and may include the mouths of the coronary arteries; the *coronary arteries* are affected often; possibly the frequency of sclerosis of these vessels secondary to high blood pressure has been underestimated, for Bell and Clawson[22] state that 68 per cent. of deaths from coronary disease are associated with hypertension; the *arteries at the base of the brain* are often very irregular in outline and lumen, and small aneurysmal dilatations in this place are not exceptional; hemorrhage and encephalomalacia result from such lesions; in many instances the cerebral arteriosclerosis occurs in the almost complete absence of vascular lesions in the kidneys and other viscera; Pal[20] and Monakow[23] have cited such cases, in defending their contention that essential hypertension is not secondary to anatomical kidney involvement; the larger *arteries of the kidneys* are ofter quite normal in essential hypertension, in contrast to the *arterioles* which usually are involved extensively; such an arteriolosclerosis is associated almost exclusively with an elevated blood pressure (Fishberg[24], Bell and Clawson[22]); arteriosclerosis of the *vessels in spleen, pancreas and other viscera* occurs but is of no clinical significance in essential hypertension; *arteriosclerosis of the extremities* is not as marked as in the senile, degenerative type of arterial disease or in diabetes, and gangrene as the result of such changes in essential hypertension is uncommon.

Arteriolosclerosis. — The term arteriole is applied to the smallest arteries immediately preceding the capillaries; the

arterioles are composed solely of muscle and endothelium; the afferent and efferent glomerular arteries of the kidney are arterioles. The changes characteristic of an arteriolosclerosis are the deposition of a layer of hyaline material immediately under the endothelium; the hyaline layer increases and narrows the lumen of the vessel; the media becomes thinned and the muscle within it undergoes fatty and hyaline degeneration; finally the blood vessel may be closed entirely, and an atrophy of the corresponding glomerulus and tubule will follow. In the kidney such changes are associated invariably with hypertension, but similar lesions may occur elsewhere, most frequently in the spleen, in the absence of hypertension (Fishberg[24], Bell and Clawson[22]). A special form of necrotizing arteriolosclerosis occurs in the kidney (see below, section on kidney).

It is generally agreed that in the case of essential hypertension arteriolosclerosis is prevalent in the kidney, pancreas, brain, retina (O'Hare and Walker[25]) and spleen and is rare in the skin, muscles, heart, lung and intestinal tract. Thus this lesion, corresponding to the arterio-capillary fibrosis of Gull and Sutton[17], is far from generalized and consequently cannot be responsible for a "peripheral resistance" that would cause an elevated blood pressure. Clinically, arteriolosclerosis is of significance only as far as the kidney, the brain and the retina are concerned. It should be remembered that an extensive arteriolosclerosis, especially of the kidney, is much more characteristic of hypertension than is the sclerosis of the larger arteries in these organs.

The *heart* becomes hypertrophied and dilated; the coronary arteries are commonly the seat of an arteriosclerosis; these lesions are responsible for about 60 per cent. of the deaths from essential hypertension. *Cardiac hypertrophy* develops as the

inevitable sequel of the increased work demanded of the heart by a prolonged hypertension. The degree of hypertrophy is usually measured by the weight; a cardiac muscle of about 600 grams, or twice the normal weight, constituting a "cor bovinum", is common; greater hypertrophy, up to 800 and even in the neighborhood of 900 grams, has been recorded. In the earlier stages of essential hypertension the hypertrophy is of the concentric type as a rule, there being no evident enlargement of the heart on clinical examination or at autopsy. The degree of cardiac hypertrophy parallels the height of the blood pressure as shown by the careful investigation of Lange and Wehner[26], Table 33.

Systolic Blood Pressure	Weight of Left Heart Compared to Normal
90–130	9.6 gms. less
130–160	56.9 gms. more
160–190 "	104.0 gms. more
190–230	204.0 gms. more

TABLE 33. — Data of Lange and Wehner[26], which show that the hypertrophy of the left heart, as measured by weight, is directly proportional to the elevation of blood pressure.

Dilatation of the heart follows the hypertrophy and *myocardial failure* finally results. This is the most frequent cause of death in essential hypertension. The dilatation and subsequent insufficiency of the cardiac muscle is brought on by two factors; the excessive strain imposed by the elevated blood pressure, and myocardial degeneration resulting from coronary sclerosis.

Myocardial degeneration, as the sequel of hypertension, has been alternately stressed and denied. Among the earliest reports on this problem is the scrupulously careful one of Aschoff

and Tawara[27], who failed to find any degenerative lesions in the heart muscle resulting from an elevated blood pressure. Most, though not all, observers are inclined to accept this statement; some believe that as cardiac hypertrophy comes on, a fibrosis develops. The clinical evidence of good response to digitalis and ability to maintain the circulation for a long period in the face of adverse conditions would certainly indicate an intact myocardium in most cases of essential hypertension. On the other hand, it is freely admitted that myocardial degeneration is often the sequel of a coronary sclerosis, which, unfortunately, is a common complication of essential hypertension. Most students of this question (as Clawson[28], Allan[29]) are of the opinion that all cases of myocardial degeneration in essential hypertension are brought about in this way. Sclerosis of the *coronary arteries*, as previously mentioned, is much more common than ordinarily supposed. According to Bell and Clawson[22], 68 per cent. of deaths due to coronary disease are associated with hypertension. The *aortic valves* may be the seat of a relative aortic insufficiency, due to a dilatation of the ascending aorta; they, as well as the *mitral valves*, are subject to sclerosis, resulting in aortic insufficiency and mitral stenosis and insufficiency. Recently speculation has attempted to account for some of the lesions in the aortic and especially the mitral valves on the basis of a sclerotic healing process following the injury caused by the stretching incident to a high blood pressure.

The *brain* in cases of essential hypertension is often the site of hemorrhage and encephalomalacia, the sequels of arterial and arteriolar changes.

The *kidneys* become sclerotic, diminished in size and their surface irregular in direct proportion to the curtailment of their

blood supply principally through the arteriolosclerosis. Macroscopically, the kidneys may be normal in appearance, they may have a slightly granular surface, or they may be markedly irregular, very much smaller than normal, with a very narrow cortex, the so-called primary contracted kidney. The microscopic lesions, principally in the arterioles, responsible for these changes, have been described already. A *summary of the pathological changes* entailed by essential hypertension is given in Table 34.

Lesions Caused By Essential Hypertension	Clinical Syndrome		Approximate Percentage Of Deaths in Essential Hypertension
Heart			
hypertrophy dilatation	myocardial insufficiency	44	
Coronary Arteries			60
arteriosclerosis myocardial degeneration	angina pectoris myocardial insufficiency	16	
Brain			
arteriosclerosis arteriolosclerosis	cerebral hemorrhage encephalomalacia		20
Kidney			
arteriosclerosis	primary contracted kidney		
arteriolosclerosis	renal insufficiency, uremia		10
necrotizing arteriolosclerosis	acute renal insufficiency and uremia		

TABLE 34. — Summary of the pathological lesions occurring in essential hypertension; some of these secondary lesions never become serious, while others may become a cause of death; whenever hypertension exists these changes are inaugurated; how rapidly and in which organ they progress, depends upon the inherent quality of the individual tissues, as well as upon the degree of blood pressure elevation, especially of the diastolic pressure.

Symptomatology

Onset. — The first symptom of essential hypertension is an elevated blood pressure. Since all the pathological lesions, the signs and the symptoms of this disease are secondary to the increased arterial tension, this necessarily must be so. The abnormal blood pressure often is discovered on life insurance examinations or health tests, as an accidental finding; the individual is entirely unaware of its presence.

The earliest complaints vary greatly and are not well defined. Often they are confounded with the symptoms of neurasthenia or those ascribed to focal infections, because they are so indefinite. Cardiac palpitation, slight dyspnea, precordial heaviness, headaches (usually slight, though they may be severe), vertigo, failing memory, fatigue, dyspeptic symptoms, nocturia and many others occur, varying according to the part of the circulatory system in which the disease is developing most rapidly. Epistaxis, or hemorrhage elsewhere, apoplexy or angina pectoris, may be the first signal of a marked hypertension.

History Form. — The symptoms of essential hypertension are necessarily varied as the pathology of the lesions of the disease are so widespread. Since the treatment of the patient must focus upon the involved organs and the functional impairment peculiar to the individual, a detailed history and physical examination are imperative. We have found that without a history form many of the details, requisite for a satisfactory therapy and follow up of each case, often are omitted; consequently, we have been in the habit of using the following history form in studying hypertensive disease and it has proved to be of great help.

HISTORY FORM FOR HYPERTENSIVE CASES:

Name:_____ Age:_____ Occupation:_____

_____19 HISTORY BY DR._____

1. HEREDITY, F. M.
   BROTHERS SISTERS
   HEART DISEASE NEPHRITIS
   CEREBRAL ACCIDENTS HYPERTENSION

2. PERSONAL ALCOHOL TOBACCO
   TEA COFFEE OTHER FLUID
   DIETARY
   GENITAL

3. PAST HISTORY (PREVIOUS OCCUPATIONS, OPERATIONS, INFECTIOUS DISEASES, MIGRAINE, GOUT, ETC.)

4. FIRST SYMPTOM (DATE, CHARACTER)

5. HYPERTENSION (FIRST NOTED, BY WHOM, READING, SUBSEQUENT READINGS)

6. CARDIAC SYMPTOMS DYSPNEA
   ORTHOPNEA EDEMA
   PAROXYSMAL DYSPNEA, DAY NIGHT
   PALPITATION COUGH AND SPUTUM
   PAINS (ANGINOID) DIZZINESS

7. RENAL SYMPTOMS, VISUAL
   NOCTURIA POLYURIA
   ALBUMINURIA EDEMA OF FACE

8. NERVOUS SYMPTOMS, CEREBRAL ACCIDENTS
   CONVULSIVE SEIZURES
   NERVOUS DEPRESSION (EMOTIONAL CRISES)
   PAINS
   HEADACHE (DURATION, INTENSITY, CHARACTER, LOCATION, TIME OF DAY)
   VISION
   VERTIGO TINNITUS
   LOSS OF MEMORY SLEEP

9. DIGESTIVE, APPETITE BOWELS
   FLATULENCE DISTENTION
   DYSPEPTIC
   OTHER SYMPTOMS

10. RESPIRATORY (SUPPLEMENT NO. 6 IF NECESSARY)

11. LOSS OR GAIN OF WEIGHT ____LBS. TO-DAY ____LBS. HIGHEST____ (19____)
    _____LBS. LOSS DURING LAST 6 MONTHS

12. FATIGUE

13. HEMORRHAGES, EPISTAXIS
    HEMOPTYSIS — HEMATEMESIS
    UTERINE — HEMATURIA
14. EXTREMITIES, ULCERS
    GANGRENE
    INTERMITTENT CLAUDICATION
15. CHIEF COMPLAINT
16. OTHER SYMPTOMS

Significance of the History and Symptoms. — The influence of *inheritance* on the incidence of essential hypertension has been discussed under Etiology.

Alcohol in moderation does not influence the blood pressure; in some persons, but not in all, the withdrawal of excessive amounts of alcohol will lower a hypertension; since alcohol is a food, it favors obesity.

The use of *tobacco* in excess lowers the blood pressure; due consideration must also be accorded the theory that the smoking habit may be a cause of angina pectoris; in producing a nervous, excitable state it may lead to a diminished circulatory efficiency in susceptible individuals.

Tea and *coffee* may exaggerate a nervous state.

Dietetic habits may have to be regulated according to the presence or absence of obesity, anemia, nephritis, myocardial insufficiency and other factors, but the high blood pressure will be influenced directly only to a slight degree or not at all by dietetic restrictions.

Genital diseases, syphilis and gonorrhea, have no bearing upon the production of hypertension. In most cases of essential hypertension the Wassermann reaction is negative. However, if these conditions are present, they must, of course, be looked after. Occasionally, a urethral stricture results in obstruction of the urinary flow and a consequent elevation of blood pres-

sure, that may be confounded with an essential hypertension. The whole symptom complex may be set aside, if the urethral stricture is relieved.

The *menopause* frequently is accompanied by a rise in blood pressure. The *toxemias of pregnancy* are prone to be followed in after life by a permanent rise of blood pressure, either with or without nephritis.

The *occupation*, both past and present, must be considered carefully, so that an opinion may be formed concerning the reaction of the patient to physical and nervous strain.

The *time of onset* of the hypertension is important, since it will allow us to judge of the progressiveness of the blood pressure and the power of the individual to meet the increased physical stress of the elevated blood pressure. As in most chronic states, prognosis is much more accurate, if these data are at hand, since the disease may be expected to progress in the future as it has in the past, and a fulminating form can be distinguished thereby from the slowly or non-progressive type.

The *cardiac symptoms* should be ascertained in great detail, for it is well known that myocardial failure is by far the most frequent cause of death in essential hypertension, and that by suitable treatment the fatal day may be postponed for a long time. Cardiac palpitation and slight precordial pressure may be symptoms of nervousness and nothing more, but they should be put in this category only after thorough investigation. Dyspnea on exertion and vertigo on assuming the upright position indicate that the cardiac power is unduly strained by the physical effort in question. Later the dyspnea becomes more marked, edema of the ankles and orthopnea develop, conditions which should be forestalled by the physician if possible. Paroxysmal dyspnea, either nocturnal or diurnal, may occur intermittently,

presumably as the result of vascular spasm in the finer pulmonary vessels, even though the heart is competent; on the other hand it may be the accompanying symptom of severe myocardial insufficiency. Pains characteristic of angina pectoris often are complained of; the frequency of death from coronary disease following on hypertension, has been stressed in the section on pathology. From my experience, I believe that it is more satisfactory to consider every case with distress even remotely resembling angina as angina pectoris, rather than to wait until the diagnosis is self-evident; if this is done, the patient is accorded more careful supervision, and the results are better.

The *kidney* is rarely subject to inflammatory lesions indicated by albuminuria, casts and red blood cells, and a renal type of edema. However, occasionally a nephritis develops in hypertensive patients. In the early stages of every case of essential hypertension and throughout the great majority of cases there are no signs of kidney involvement in the urine in the form of albumin or casts, nor is there the slightest indication of any impairment of renal function in the blood chemistry or on other tests. The arteriolosclerosis and arteriosclerosis of the kidney, which occur in most instances of essential hypertension, do not, in their early stages, furnish any clinical clues to their existence. When the arterioles and possibly some of the arteries become partially or completely occluded, and a sclerosis of the kidney develops, the much quoted "trace of albumin" and a few hyaline casts may make their appearance, but the degree of kidney involvement and danger to the patient can be estimated only by the blood chemistry, specific gravity and other procedures for measuring or testing renal function. In about ten per cent. of all cases of essential hypertension a retention

uremia occurs. This may develop gradually as the sclerosis of the kidney advances, but sometimes it is of the fulminating type, corresponding to a necrotizing arteriolosclerosis of the afferent glomerular arteries and a rapid shutting off of a large part of the glomerular circulation. As a rule this form of nephritis comes on suddenly and for no known reason in patients who have had a marked elevation of systolic and diastolic blood pressure for a long time. (Dr. Paul Klemperer has furnished the information on which the statements concerning acute uremia are largely based.)

The *nervous symptoms* fall into two categories, those associated with the feeling of general malaise and apprehension and those due to arterial lesions in the brain and the retina.

Symptoms resembling those of functional nervous disorders, including depression and restlessness, are common. It is often exceedingly difficult to determine whether they are due to the diminished circulatory efficiency of the cerebral arteries, or whether they are indicative of a sensitive personality, reacting to the unaccustomed irritation of a pounding heart and throbbing arteries. Lead cap headache, globus hystericus, tearfulness, volubility, exaggerated emphasis of very minor situations and other similar manifestations, that make these patients a burden to themselves and their friends, are present only too frequently. In many instances these changes certainly are of functional origin, for there are countless sufferers from the severest type of essential hypertension that never lose their self control nor register such complaints. Sleeplessness is probably the most important of all these symptoms because good, deep sleep, free from harassing dreams, is needed if the blood pressure is to diminish to any extent during the twenty four hours, and insomnia thus means the loss of the best opportunity to relieve

the strain upon the circulation. These functional, nervous disturbances should be analyzed carefully, since they require attention as well as the other and very different aspects of essential hypertension.

Loss of memory and vertigo are common. They may be associated with a more or less diffuse cerebral arterial involvement that in itself leads to no immediate catastrophe; the loss of memory, slight at first, often progresses, and with it develops a lack of judgment and discrimination, rendering such individuals unfit to continue in positions of trust and responsibility.

Palsies may be transient or permanent; convulsive seizures may occur. It is accepted generally now that spasms may occur, depriving a given area of blood for a few moments; a transient paralysis, loss of function, twitchings or convulsions of varying extent are the result. Sir William Osler was among the first to observe such vascular spastic phenomena with the ophthalmoscope and led the way to the acceptance of the idea that such an intermittent contraction of arteries and arterioles is not uncommon; when it occurs in the brain, where there is very little compensatory circulation from the adjoining arteries, and where the involvement of small areas can produce far reaching effects, the symptoms are likely to be very striking. Many of these angiospastic attacks last only for a moment; a mumbling of words, due to heaviness of the tongue, that interferes with a single sentence, or a weakness of one side of the face, of a limb or a part of one for a few hours, may be the only symptoms. Such attacks may never return; they may manifest themselves at intervals in the same or other areas, and finally they may be succeeded by a thrombosis or hemorrhage that induces a more lasting effect. One of my patients at different times had a facial paralysis, loss of speech and the palsy

of one leg, each lasting about fifteen minutes. These episodes took place about twenty-four years ago, and there have been no recurrences since that time.

Hemiplegia, unilateral or crossed, is the most frequent result of hemorrhage or thrombosis. The onset may be signalized by weakness and mumbling for a few days, though a sudden, unheralded occurrence of the paralysis is the more usual course of events. The apopleptic condition is prone to be accompanied by loss of consciousness and shock. With the increasing intracranial pressure, the heart often fails and a fatal termination may occur almost immediately, or in the course of a day or two. However, in quite a remarkable way patients apparently moribund sometimes recuperate and return to normal, except for the paralyzed muscles. The palsies nearly always show some improvement; sometimes they disappear within a few days, except for a slight residual weakness; in obstinate cases improvement may be expected to take place for six or even nine months after the stroke has occurred; exactly how far the original power will be regained cannot be prognosticated according to any given criteria, but there is room for optimism concerning the outlook.

Headaches in essential hypertension vary greatly, both in regard to the location and character of the pain. The frequent occurrence of head pains, characteristic of functional nervous disorders, has been alluded to already. In addition, there are the headaches probably associated with the cerebral arterial degeneration. These may be due to the effects of the diminished blood flow in the partially occluded vessels, or to small hemorrhages, or to the pressure exerted by tortuous and dilated arteries. These headaches may be mild or severe; they may be as distressing as those characteristic of brain tumor; they may

come irregularly, lasting a few hours or a day, and not reappear for weeks or months; Theodore Janeway[30] observed that frequently they began in the early morning hours, waking the patient at about five A.M. and continuing for five or six hours and then ceasing only to reappear the next day at the same time; this cycle Janeway[30] believed so frequent and so characteristic that he called it the "hypertensive headache". This sort of cycle is often met with, but there is no set rule about the time of day at which the headaches appear or disappear. In some patients they come on suddenly, persist for a period of weeks and then disappear as mysteriously as they arrived; in others they may begin intermittently and increase in intensity and duration until they become almost unbearable and practically constant. A diagnosis from brain tumor in some of these cases is almost an impossibility, especially since the retinal picture is very much the same at times in the two conditions.

Diminished vision usually is associated with retinal involvement, though it may, on occasion, be the result of a lesion in the central nervous system.

The *intestinal symptoms* are commonly those incidental to the life of any human being. Occasionally there is an arteriosclerosis of the intestinal vessels that brings about more severe manifestations. I witnessed the autopsy on a case of essential hypertension, which had undergone two European cures for duodenal ulcer, although there were no signs of it in the intestinal mucous membrane. Pal's[31] description of intestinal crises associated with hypertension in locomotor ataxia and lead poisoning may well have their counterpart in essential hypertension, if the corresponding angiospasm occurs.

The hypertensive patient may be thin or obese, according to his diet, exercise and other habits. As far as *weight* is concerned,

there is only one fact to be remembered and this is, that a loss of flesh often is indicative of a generalized arteriosclerosis that interferes with tissue nutrition, and this is a poor prognostic sign.

Hemorrhages from arteriosclerotic arteries on the physiological exterior of the body are common. Epistaxis is the best known of these, though the bleeding may originate from the intestinal or urinary tract, from the uterus or elsewhere.

In the *extremities* angiospasm, producing intermittent claudication, with a temporary loss of power and intense pain on walking or other exertion, occurs occasionally. Marked thickening, calcification and roughening of the arteries, followed in some instances by gangrene, is more common in the degenerative form of arteriosclerosis associated particularly with diabetes mellitus than it is in essential hypertension.

Physical Examination and Signs

A certain type has been described as liable to hypertension. This is, physically, the thick-necked, plethoric individual, dynamic in personality, lacking in sensitiveness, who works hard and plays hard, and knows no relaxation. Such persons are oblivious of any irritation which the hypertension may impose and are often only diagnosed when they crash because of apoplexy, heart failure or angina pectoris. Then the sudden dramatic change from apparent super-health to invalidism focuses attention upon this type as the characteristic subject of essential hypertension. In scanning all hypertensive patients it appears that persons of less heroic physique and habits are very common. They are not as insensitive to the stress of an elevated pressure and seek medical aid earlier. They are often thin, appear tired, are nervous, have a hunted look and lack self confidence. The

former and the latter represent the extreme types susceptible to hypertensive disease; regarding them as such one could conclude that, as far as constitutional standards are concerned, there are at present no characteristic attributes symbolic of a hypertensive diathesis.

A thorough routine physical examination should be carried out on each patient. In addition, since essential hypertension results in certain well recognized secondary pathological lesions, especial attention and particular interpretation must be accorded such signs. It is only these that will be discussed.

Blood Pressure. — When an elevated blood pressure is determined, the patient should not be immediately classified as an instance of "high blood pressure", "hypertension", or "essential hypertension", without consideration of the following:

1. The manometer readings should be compared with the average normal blood pressure readings for age (Tables 6, 7 and 8, Chapter II). Note the pressure at various ages:

Age	Blood Pressure		Pulse Pressure
	Systolic	Diastolic	
15	106	68	38
60	135	89	46
80	175	94	83

Thus with advancing years the systolic pressure rises markedly, the diastolic increases, though less rapidly, and consequently the pulse pressure rises. These changes in the blood pressure are ascribed to the effect of increasingly rigid arterial walls, accompanying the arteriosclerosis which is the physiological expression of growing old.

2. A high systolic and a comparatively low diastolic pressure,

besides being a sign of loss of elasticity in the arteries, may be the result of an increased cardiac output, which is especially characteristic of aortic insufficiency, hyperthyroidism or heart block. Any pulse pressure above 60 should be a warning to consider carefully the possibility of these diagnoses.

3. An elevated blood pressure may be a constitutional characteristic of an individual present throughout his entire life (Tables 10 and 11, Chapter II). These instances differ from essential hypertension in that the blood pressure does not rise progressively from year to year and does not reach a level which threatens the patient's life (Table 12, Chapter II). It is impossible at the present moment to differentiate these cases except by determining the trend of the blood pressure by continuous observation for a year, or longer, if necessary.

4. Another aspect of the foregoing is that the limits of normal blood pressure values do not conform closely to the average standards set up by life insurance statistics (Tables 13 and 14, Chapter II). Medical directors of life insurance companies deal with large groups, but we, as physicians, must consider individuals and individual variations. Deviations from the accepted standard average occur especially among the systolic blood pressure readings of old age and of women after the menopause (Table 9, Chapter II).

5. A high blood pressure, considerably above the characteristic normal for the patient, may be found at the initial examination. As the nervous tension associated with the medical visits subsides, the blood pressure often diminishes. An extraordinary instance of this sort was related to me by Dr. Irving Somach: a dispensary patient, a woman of 53, was found to have a blood pressure of 230/120 and two weeks later a reading of 160/100. Here, as usual, the systolic pressure

dropped far more than the diastolic. Sometimes I have found two months or more of observation needed before such "spontaneous" drops of blood pressure became complete, that is, until the lowest level characteristic of the individual was reached (Table 23, Chapter VII). It is evident, therefore, that the diagnosis of hypertension should be made cautiously. Furthermore, there are a considerable number of cases with marked fluctuations in blood pressure, due to intermittent peripheral vaso-constriction, that are not true instances of essential hypertension (Tables 30 and 31, Chapter VIII).

6. A low or normal blood pressure under certain conditions does not exclude the possibility of hypertension. Such depressed states of arterial tension are found especially in moribund patients (Tables 4 and 5, Chapter I), in cases of malnutrition (Table 28, Chapter VII) and in old people with weak heart muscle.

7. Only when both diastolic and systolic pressures are elevated should we make the diagnosis of essential hypertension. Usually in this disease, over a period of months, both the blood pressure values observed have a tendency to rise. When the diastolic readings reach a level of 120 to 130 mm. of mercury, the case may be considered to be of the severe type of the disease.

The heart is hypertrophied in every case of essential hypertension. In the earlier stages of the condition this hypertrophy is of the concentric type, that is, on physical examination, the size of the heart is normal and the increase in the cardiac muscle is diagnosed from a heaving apex beat and the fact that an elevated blood pressure exists. Such a concentric hypertrophy may persist for many years; how long it continues without superadded signs of cardiac dilatation depends more

upon the inherent quality of the heart muscle than upon the height of the blood pressure itself. This conclusion may be drawn from the fact that cases of marked hypertension of long duration frequently show a concentric hypertrophy of the heart, whereas only slight elevations of blood pressure, especially in poorly developed individuals, may result in cardiac dilatation. The innate character of the cardiac muscle shows itself in the widely divergent weights of the hypertrophied hearts in hypertensive conditions; these hearts may vary anywhere from 450 to 900 grams in weight and yet be within the expected range.

When the initial concentric hypertrophy of the left ventricle has continued for some time and has reached its maximal increase for the particular individual, a time of cardiac decompensation often follows, due to the stress of the hypertension. Once this has begun, it is likely to advance, though very slowly, and frequently terminates the illness. The progress of the myocardial insufficiency is very gradual as compared with that in valvular disease, because as a rule there is no myocardial degeneration in hypertension, such as generally accompanies endocardial lesions and renders the action of the heart muscle correspondingly less effective. The successive changes in the heart in essential hypertension and the accompanying physical signs may be presented briefly in a chart. (See Table 35.) It should be understood that in this table, the possibility of coronary sclerosis or of sclerosis of the aortic or mitral valves has been omitted; these will be considered subsequently. If the physician notes these successive stages in the effect of hypertension on the heart muscle, he has the surest guide to the regulation of digitalis therapy and physical exercise. Death, as a result of myocardial insufficiency, often occurs before the right ventricle dilates, that is, with left ventricular insufficiency only;

this seems to be perhaps the more frequent occurrence; the relative power of the muscle tissue in the right ventricle determines the course of events.

Disease of the *coronary arteries*, as mentioned in the section on pathology, is more common in association with essential hypertension than with all other diseases combined. Both

Successive Myocardial Changes	Corresponding Clinical Signs
1. Concentric hypertrophy of left ventricle.	Aortic second sound accentuated, possibly ringing. Apex beat heaving in character.
2. Dilatation of left ventricle.	Precordial dullness enlarges to the left and downward.
3. Relative insufficiency of the mitral valve.	Systolic murmur at the apex; progressive dyspnea.
4. Concentric hypertrophy of right ventricle.	Pulmonic second sound accentuated; as left ventricular insufficiency is more marked, the pulmonic second sound may become even louder than the aortic second sound; progressive dyspnea.
5. Failure of the right ventricle; relative tricuspid insufficiency.	Precordial dullness is enlarged to the right; dyspnea is often greatly relieved; edema of the lower extremities and enlargement of the liver.

TABLE 35. — Progressive changes of the heart muscle and the corresponding clinical signs in essential hypertension. This does not include the effects of coronary sclerosis or sclerosis of the aortic and mitral valves which are frequent complications.

sclerosis and angiospasm, separately, or in combination, may interfere with the coronary circulation and produce angina pectoris, whose symptoms and signs do not differ from those usually accepted as characteristic for this condition.

The frequent association of hypertension with the valvular lesions, *aortic insufficiency* and *mitral stenosis*, has been noted for some time; recent comment has revived interest in this relationship.

The mechanical effect of aortic insufficiency upon the blood propulsion, as is well known, raises the systolic and lowers the diastolic pressure. Boas and Fineberg[32] believe that in many instances the hypertension cannot be accounted for in this way, and that the high blood pressure is responsible for atherosclerotic aortic insufficiency. It is logical to assume that, if the strain entailed by hypertension causes sclerosis of the ascending aorta and the coronary arteries, the aortic valves also may become affected. I have watched several hypertensive patients in whom an aortic insufficiency developed apparently on this basis. It is worthy of note that the feeling of discomfort attendant upon very high blood pressure may be relieved, when aortic insufficiency comes on. Occasionally, a relative insufficiency of the aortic valves is found; the dilatation of the ascending aorta may include the aortic ring and thus bring about this functional heart change. I have seen a few instances in which, although there were definite signs of aortic insufficiency during life, the aortic valves were perfectly normal at autopsy, and the signs could only be explained on the basis of a relative aortic insufficiency.

Both Boas and Fineberg[32] and Levine and Fulton[33] find that hypertension and mitral stenosis often coexist, especially in people over 40 years of age, in which group this combination occurs in about fifty per cent. Levine and Fulton[33] believe that all these instances of mitral stenosis have had rheumatic cause, and that the effect of the same constitutional dyscrasia upon the vascular system brings on a hypertensive state. Boas and Fineberg[32] credit the mitral stenosis not only to a rheumatic but also to an atherosclerotic origin; they also reject the idea that such valve lesions are caused by the strain of the high blood pressure. It is a little difficult to understand the differ-

ence between the aortic and mitral valves in this regard; if an elevated blood pressure can effect sclerosis of the aortic valves, it would seem reasonable to suppose that an increased tension within the left ventricle, which exists in essential hypertension with its high diastolic pressure, would have the same effect on the mitral cusps.

Arteriosclerosis of the aorta throughout its entire length is found frequently at autopsy in cases of essential hypertension. Clinically, it makes itself evident only by the presence of a pulsation in the suprasternal notch and an increase of the retromanubrial dullness, which indicate a lengthening and widening of the ascending aorta. These signs are often found when on X-ray examination or at the post mortem table the aorta is of normal dimensions. This discrepancy is more apparent than real and can be explained by the fact that an aorta, which retains its elasticity, may be both lengthened and widened during cardiac systole and resume its normal dimensions during diastole or after death. The pulsation felt in the suprasternal notch is rarely due to the aorta itself but to the great vessels arising from the aorta in this region. The ringing quality, which often characterizes the aortic second sound, is ascribed to the presence of a dilated ascending aorta.

Signs referable to the *kidney* are usually negative, but because of their importance, when severe nephritis occasionally does manifest itself, they should be given particular consideration in every case of essential hypertension. In the early stages of hypertensive disease no kidney lesions are present. As a result of the persistence of the high blood pressure over a period of years, arterio- and especially arteriolo-sclerosis of the kidney is engendered to a varying extent; atrophy and sclerosis of the renal tissue develop in direct proportion to the severity of the

vascular lesions, and there is corresponding degree of contraction of the kidney. This form of nephritis, the primary contracted kidney, gives no satisfactory evidence of its existence on routine clinical examination; except for a trace of albumin and a few hyaline casts, which in themselves cannot be regarded as particularly significant, there are no signs worthy of note. The sclerosis of the kidney does not give rise to marked albuminuria, hematuria or granular and epithelial cell casts as do the other forms of nephritis. Its progress is not spectacular but very insidious, and its severity must be judged by tests for renal function, such as studies of urinary specific gravity, phenolsulphonephthalein excretion and especially the blood chemistry. Only by these means can the extent, to which the sclerosis of the kidney has advanced, be judged. Such tests should be carried out as routine diagnostic measures in every case of essential hypertension and should be checked up at approximately yearly intervals. In most instances the kidney function is normal or nearly so. The fact that only ten per cent. of deaths in essential hypertension are due to renal complications makes this evident; however, it is necessary to be on the watch for signs of the progressive development of a primary contracted kidney of sufficient severity to cause retention uremia, even though it occurs only occasionally.

A true inflammatory nephritis with marked albuminuria and edema may accompany essential hypertension. Such a nephritis may be super-imposed upon a hypertension; on the other hand, the elevated blood pressure may be secondary to the nephritis. It is often extremely difficult to unravel this sequence.

As mentioned under pathology, in cases of essential hypertension of long duration and of rather high diastolic blood pressure, acute renal insufficiency and retention uremia, as the

result of necrotizing arteriolosclerosis of the afferent glomerular vessels, may come on rapidly for no apparent reason and prove fatal.

Changes in the *fundus oculi* are nearly always present in essential hypertension. It is very remarkable to see what different interpretations have been put upon these signs, especially in correlating them with clinical disease. A few salient facts are worthy of note. O'Hare and Walker[34] claim that every instance of hypertensive disease is associated with retinal arteriosclerosis; they go one step further in their conclusions in believing that arteriosclerosis of the retinal vessels indicates a previous elevation of blood pressure even where this does not exist at the moment; finally, they find that patients with advanced decrescent arteriosclerosis, as evidenced during life in the radial and brachial arteries, may have absolutely normal retinal vessels, provided there is no increase in arterial tension. These statements I believe are approximately correct. They lay stress on the frequent association of retinal arteriosclerosis and hypertension. Arteriosclerosis of the retina is described briefly and accurately by Martin Cohen[35], who has done splendid work in this field, as follows:

"The suggestive signs are: (1) uneven caliber and undue tortuosity of the arteries, (2) prominence of its central light streak, (3) light color of the arteries, (4) dilated and tortuous veins.

"The pathognomic signs are: (1) the arteries are decidedly contracted and tortuous, especially the secondary and tertiary branches; (2) white stripes bordering the arteries (periarteritis), or complete obliteration of the lumen (endarteritis), which appearances produce the silver wire aspect; (3) alternate contraction and dilation of veins due to areas of endothelial

proliferation and indentation of veins from a varying amount of mechanical pressure when crossed by hyalinized arteries; the arterial crossing of the veins by the arteries, or vice versa, produce the following important effects on the vein, depending upon the degree of arteriosclerosis: (1) slight flattening, (2) pushing it aside, (3) direct indentation."

The above changes are followed by hemorrhages; a peculiar mottled appearance of the retina with a black pigment resembling coal dust scattered over a butter yellow or whitish glistening background, which has been called "moth eaten retina"; and round or oval white areas of degeneration with definitely outlined margins. The appearance of these lesions marks the change from a retinal arteriosclerosis to an arteriosclerotic retinitis.

Later on, especially in cases with a high diastolic pressure and a poor prognosis, classified as malignant hypertension by Keith, Wagener and Kernahan[36], a picture develops closely resembling that generally accepted as characteristic of an albuminuric retinitis or of brain tumor. Papilledema, slight or severe, with as much as six diopters swelling of the optic disc, cotton wool exudate, edema of the retina, marked hemorrhages, all are present. This process, according to Keith and his collaborators[36], progresses to enter a final stage in which the disc has become definitely pale, and only blurring and increased glial tissue remain as evidence of the previous edema; atrophy has replaced the edema of the retina, and only a few residual small punctate exudates may remain.

Frequently, though by no means invariably, the pathology of the retina may be regarded as similar to that of the cerebral vessels (Cohen[35]). A knowledge of the lesions existing in the finer blood vessels of the retina and, by inference, of the other

tissues, can be obtained during the life of the patient only by the ophthalmoscope.

In the vast majority of cases of hypertension the *hemoglobin* and *red cell count* are normal. However, in many instances, a study of the blood count may furnish a clue or confirm clinical impressions with regard to whether the kidney, heart or cerebral blood vessels are involved. In the case of the kidney, a progressive anemia parallels the degree of impairment of renal function. In a series of cases of hypertension with associated renal insufficiency the following average data were obtained: hemoglobin 88 per cent. with 4,848,000 red cells, when no impairment or a slight impairment of kidney function was found; 81 per cent. with 4,763,000 red cells in the cases with moderate involvement, and 65 per cent. with 3,775,000 red cells where the kidneys showed marked or maximal insufficiency.

If congestive myocardial insufficiency supervenes, the hemoglobin is lowered much more markedly than is the red cell count, which is "artificially" increased because of peripheral stasis, the result being an "anemia of hemoglobin only", as, for example, an average hemoglobin percentage of 77 per cent., and a red cell count of 4,881,000.

In most of the cases in which the cerebral blood vessels have been affected by the increased blood pressure, a high normal or "polycythemic" blood count obtains, no matter what the degree of renal insufficiency may be. Counts of 91 per cent. hemoglobin, with 6,006,000 red cells, or 110 per cent. hemoglobin and 5,152,000 red cells, may be cited as examples.

Prognosis

The most reliable basis for prognosis lies in the height of the *diastolic blood pressure*. An elevation of merely the systolic

pressure is compatible with an indefinite span of life. It has been mentioned that especially in old people and in arteriosclerotic individuals the systolic reading may be in the neighborhood of 200 mm. of mercury, while the diastolic pressure remains approximately normal. It is these cases that have warranted the observation that persons with a blood pressure of 200 or higher have been known to live for 30 or even 40 years. A diastolic pressure of 110 approaches the danger line, one of 120 enroaches on it, and, I believe, we can freely subscribe to the general application of Phillips'[37] observation that of cases whose diastolic blood pressure was 130 or over, approximately 55 per cent. lived less than two years. There are many exceptions to this rule. One case reported by Paullin[38] is particularly noteworthy; that of a female patient, still living, whose diastolic pressure has ranged between 129 and 125 for 16 years. In Paullin's[38] series it is very evident that the mortality was directly proportional to the diastolic pressure.

Sex. — All observers agree that the mortality of women is much lower than for men. It is probable, as shown in Chapter II, that women are prone to have an elevated blood pressure at the systolic phase of the cardiac cycle only, and that the higher diastolic pressure in hypertensive men is the factor responsible for the greater fatality in the male sex.

The *pathological changes* effected by the hypertension have a distinct bearing on prognosis. They naturally differ in each individual according to the particular response of the tissues. In the order of their importance, they are: the heart, the brain and the kidneys.

Many signs in the *heart* have been ascribed a prognostic significance. A summary of these findings, as taken largely from the writings of Willius[39], Pardee[40], Horine[41], and Hepburn and Jamieson[42], is as follows:

1. From two to five years is the average duration of life when manifest evidence of *congestive* or *anginal failure* arises in hypertensive heart disease.

2. *Electrocardiogram.* — This, in my experience, has been negative in more than half of the cases, except for left ventricular preponderance, which in itself is of no great clinical significance.

a. *Varying grades of heart-block.* — This indicates some myocardial change, but an individual with this sign may carry on for years.

b. *Peak-notching of the QRS group* renders prognosis more grave.

c. *Low voltage of the QRS group* renders prognosis more grave.

d. *Inverted T waves*, not dependent on digitalis, and except for a negative T in lead III alone, which has no prognostic significance, is not a favorable finding; 50 per cent. of such cases die within 12 months. 42 per cent. of "T wave negativity" occurs in hypertensive states, indicating a very frequent association between them. (It is a common experience to have patients with this electrocardiographic anomaly live very much longer than 1 year.)

e. *Coronary T waves*, die in less than 1 year.

f. *Bundle-branch block*, an exceedingly grave symptom; death usually occurs in less than 18 months.

g. *Auricular flutter* adds to the gravity of the prognosis.

h. *Auricular fibrillation* adds to the gravity of the prognosis.

i. *Sinus arrhythmia*, no prognostic significance.

3. *Pulsus alternans* is a definitely bad prognostic sign.

Signs of *cerebral involvement*, if due to thrombosis, rupture or spasm of a single vessel, are often compatible with an indefinite

period of life, if the original attack is not fatal. It is impossibl to foretell whether a repetition of such an event will occur, o how long it may be delayed. Signs of encephalomalacia, whe once initiated, are likely to be progressive, and it is my im pression that they are usually fatal within two to five years.

Retinitis, of the variety described by Keith, Wagener an Kernohan[35], that is, characterized by marked edema and exu dates, accompanies a hypertension malignant in its effect an is likely to be a signal of death within two years. Most o these cases apparently die of cerebral complications. An arte riosclerosis and a few hemorrhages only of the retina are not s serious and in themselves should not be regarded as bad prog nostic signs.

The *kidneys* are but rarely the cause of death in essentia hypertension. Only about ten per cent. of these cases die o renal insufficiency; in Christian's[42] series, the deaths from ure mia or associated with extensive chronic nephritis amounte only to 4.5 per cent. Even so, it is necessary to watch for suc possibilities as a fatal degree of renal insufficiency may develo very rapidly within a year or even a few months.

Treatment

The treatment of essential hypertension requires infinite tac and resourcefulness on the part of the physician and coöperativ confidence on the part of the patient. Cases with a diastoli blood pressure below 100 mm. of mercury usually need ver little active interference. When the diastolic readings go abov 100, the physician's best efforts should be made to control th arterial tension and to prevent the occurrence of sequelae, as fa as possible. The principles upon which the therapeutic pro cedures rest have been discussed in Chapter VII and elsewhere

here the methods of treatment will be taken up only from the point of view of their practical application.

Nervous relaxation should be obtained as far as possible. Business and occupational worries should be so adjusted that they involve a minimum of strain. It is usually best not to set aside all vocational efforts but only to curtail and regulate them. Frequent, short vacations are advisable. two or three weeks every two or three months are an excellent formula and prove more beneficial than longer periods that often become monotonous. The more intricate problem of remedying incompatibilities in the home life is an arduous and thankless task for the doctor, but often a very necessary one. It should be borne in mind that nervousness and irritability may be a sign of advancing cerebral arteriosclerosis that cannot be treated except by relieving such patients of the responsibilities that they are no longer capable of meeting satisfactorily.

Rest can be prescribed in more exact terms. One hour's nap after lunch, or before dinner, if the noon hour is impracticable, and 8 hours' rest in bed at night, is the minimum that should be asked for. In marked cases every, or every other, week end in bed, or a week in bed every two or three months, and this in seclusion, away from business or hordes of anxious friends and relatives, will furnish more effective relief. It is much safer to have too much rest than too little. "The fact that pressures rise again to former levels after the patient gets about does not disqualify the procedure. For a time at least the strain has been relieved and circulatory reserve is improved thereby" (Elliott[44]).

Sleep, of a good, sound kind, is very essential. If sleep is restless, disturbed by dreams, or if there is insomnia, the time honored household remedies of hot bathing, a warm glass of

milk or some bland food or drink before going to bed may suffice to remedy the situation. If they do not, bromides, chloral, the barbituric acid compounds or other favorite hypnotics must be resorted to in sufficient doses to produce sleep. Care should be taken, of course, that the drugs do no harm, but that danger is more theoretical than real in essential hypertension.

The *diet* must be regulated according to many indications, and no routine procedure can be advocated. If there are no complications, a sensibly moderated menu both as regards quantity and quality of food is all that is required.

Regulation of weight through diet is extremely important. If cardiac overstrain is to be anticipated, *obesity* should be avoided at all costs, and a few pounds under the average normal weight for height, age and sex should be the objective. In prescribing anti-obesity diets, it is important to realize that foods high in protein content, including both red and white meats, do not raise blood pressure, but that carbohydrates and fats tend to increase weight and thus add to the heart's burden. In effecting weight reduction, the loss of fat and the retention or even gain in muscular and glandular tissue is aimed at; hence the drastic, simple diets, such as a pint of milk a day, one starvation day at intervals, etc., are contra-indicated. If the food is measured, the day's ration should contain 60 to 80 grams of protein, an equal amount of carbohydrate and enough fat to make 1000 or 1200 calories. However, quantitative diets are irksome and are usually not necessary. In telling patients about these food prescriptions, it is only proper to warn them that even comparatively slight indulgence in the forbidden articles of food is likely to nullify the effort of disproportionately long periods. A weight-reducing diet that has proved satisfactory is the following:

Breakfast:

1 medium sized orange
or 1 medium sized apple
or ½ small grapefruit
or any fruit cooked without sugar
1 egg, boiled or poached
Tea or coffee with 1 tbsp. cream

Lunch:

Clear soup with vegetables from list 1
Lean meat or fish, 1 generous helping
Vegetables from list 1 as desired
Vegetables or fruits from list 2, two heaping tbsp.
2 Uneeda biscuits or 1 slice of bread
Clear tea or coffee

Dinner:

Clear soup with vegetables from list 1
Lean meat or fish, 1 generous helping
Vegetables from list 1 as desired
Vegetables or fruits from list 2, two heaping tbsp.
2 Uneeda biscuits or 1 slice of bread
Fruit as for breakfast

Use mineral oil instead of olive oil or butter for salad dressings, frying, etc.
Use saccharine as desired.

Vegetable List No. 1		*Vegetable List No 2*	
Asparagus	Lettuce	Pumpkin	Apples
Asparagus tips	Radishes	Turnip	Grapefruit
Broccoli	Rhubarb	Kohlrabi	Strawberries
Brussels sprouts	Sauerkraut	Beets	Blackberries
Cabbage	Sorrel	Carrots	Pineapple
Cauliflower	Spinach	Corn	Peaches
Celery	String beans	Mushrooms	Pears
Cucumbers	Swiss chard	Green peas	Watermelon
Egg plant	Tomatoes	Artichokes	Apricots
Endive	Vegetable marrow	Parsnips	Blueberries
Beet greens	Water cress	Lima beans	Cherries
Leeks	Wax beans	Raspberries	Currants
		Huckleberries	Gooseberries

Some patients do poorly when they lose weight; they say they feel weak, they complain of the appearance of wrinkles and often grow so introspective that efforts at weight reduction have to be discontinued or modified. Walking, or any regular exercise is of great aid in reinforcing the effect of anti-obesity diets.

A high percentage of *hemoglobin* and a high *red blood cell count* may be reduced by a restriction of the protein foods; on the other hand, malnutrition and anemia, if due to a faulty diet, can be corrected by a high protein diet. Malnutrition lowers the blood pressure, but naturally renders the tissues less resistant to the strain of hypertension. It is difficult to state clearly where to find the right balance here. A good rule to follow as far as possible is to strive for a hemoglobin of 85 per cent. and a red blood cell count of 4,500,000.

Salt restriction in moderation should be advised. That is, a sensible amount of salt should be used in cooking and at the table, on soft boiled eggs, etc., but salty foods, bacon, salt codfish, corned beef, etc., should be avoided. About 5 to 6 grams of salt may be present in the 24-hour urinary specimen without causing any trouble. If there is myocardial insufficiency, with or without edema, an absolutely salt-free regimen should be insisted on; that is, the preparation of all foods without salt, salt-free butter, salt-free bread; all meat and fish boiled and the water poured off; no gravies; no meat soups; vegetables preferably boiled and the water poured off; no cheese, no milk; a small amount of cream only. Frequent attacks of angina pectoris, renal edema or an advanced degree of renal insufficiency call for a similar curtailment of sodium chloride. When extreme restriction has been adhered to for some time, the patient may become more or less prostrated, and it is then necessary to make corresponding concessions in the salt intake.

The amount of *fluid* taken has little effect on blood volume or blood pressure. Instead of restricting the fluid intake, the physician must meet the greater difficulty of making the patients drink enough to promote normal action of the skin, the

bowels and the kidneys. One and a half to two quarts a day should be the minimum; much more than that is usually of no benefit and causes the inconvenience of polyuria. Where there is renal insufficiency with low specific gravity, polyuria becomes necessary, if kidney function is to be maintained at its best, but this situation is rarely met with. The kind of fluid intake is another matter. Water and fruit juices are always acceptable; aerated waters, ginger ale, etc., are inadvisable if they cause distention of the stomach, which is to be avoided in dyspeptic conditions, angina pectoris or where there is impaired cardiac power; coffee and tea may be allowed, short of amounts to cause nervousness or insomnia, and often they help headaches a great deal; decaffeinized coffees may fill a want for some of these patients; alcohol is of no advantage in this condition; in large amounts it promotes obesity and may raise blood pressure, but in some individuals the agony of withdrawal does more harm than the continuance, and they may be allowed a restricted amount, not over two drinks of liquor per day; milk is contra-indicated where obesity threatens, but otherwise it may be used, and even prove beneficial, if there is malnutrition. In myocardial insufficiency, edema of cardiac or renal origin, the fluid intake must be restricted without any regard for the hypertension.

Therapy of the intestines in essential hypertension, as in other conditions, has been accorded a somewhat exaggerated importance; that is, there should be one or two movements a day and the evacuation should be free and take place without undue straining. The last is important as the effort of expelling a constipated movement is often the occasion for an apopleptic attack. Aloes, rhubarb, phenolphthalein or resina podophylli, in suitable amounts, combined with 15 mgm. (1/4 grain) of

extract of belladonna, furnish an excellent bedtime capsule that can be taken advantageously for years. The use of "nature's laxatives", that is, the eating of bran or excessive amounts of fruit and green vegetables, the frequent dosing with paraffine oils, agar-agar and seeds, favors abdominal distention and thereby tends to interfere with the action of the heart and to impede the circulatory flow. Therefore, these popular laxative measures should not be resorted to inadvisedly. Drastic purging at intervals by castor oil, or by blue mass or calomel, followed by a saline cathartic, often is beneficial. It is especially indicated when congestive symptoms of the head or lungs appear. Some clinicians advocate the use of these purges, systematically, once or twice a week. Care must be taken that prostration does not result, especially in patients on the brink of cardiac failure. The weekly, bi-weekly or even daily routine use of colonic irrigations has found some favor. Too frequent recourse to this procedure may cause a marked physical weakness. Some patients derive great satisfaction from intestinal lavage, and when carried out once or twice a week it does not harm robust individuals; when the intestines are unduly distended, a colonic irrigation, ordered occasionally according to symptoms, may be very helpful.

Exercise is often forbidden entirely in essential hypertension, because of the desirability of absolute rest. But a body that relaxes continuously loses cardiac reserve and the power to regulate blood pressure, and hypertension may result or be aggravated under such circumstances. For these reasons, exercise is advisable. It should be taken according to a definite program, if possible, every day; spasmodic exertion at week ends or at other irregular intervals is undesirable; it should never be so severe as to cause dyspnea of any moment; walking

one, two, or more miles a day, not as part of business or incidental to shopping, but with the idea of devoting a definite time to this task, often suffices; setting up exercises, resistance exercises with massage, will serve the same purpose; in the more vigorous, golf or horseback riding may be allowed; if the hypertensive patient is young and in good physical condition, more strenuous exercise, such as tennis, swimming, etc., may be permitted, but these activities must be supervised very closely so that myocardial insufficiency will not be induced; if the diastolic pressure is above 110 mm. of mercury, it is unwise to allow any more strenuous exercise than a daily two hours of golf. Rappaport[45] recently has concluded that "hyperventilation exercises, carried out in the form of an intensive and prolonged training in deep breathing, are capable of bringing about marked reductions of pathologically increased blood pressures."

Drugs and *specific remedies* for the purpose of lowering or controlling hypertension are very numerous. They may be conveniently divided into three classes; vasodilators, sedatives and specific remedies. The *vasodilators* lower blood pressure by widening the peripheral vessels. In true essential hypertension this effect has not proved to be sufficiently prolonged to be of clinical value, nor is the cause of this condition, the hypertonicity of the larger blood vessels, controlled thereby. In the instances of high blood pressure brought on by peripheral vasoconstriction, usually intermittent in character, the vasodilators are effective and valuable. The well known use of nitroglycerin in relieving the symptoms of angina pectoris is an example. It would seem that in general the vasodilators have not been used as much as they should be in the emergency treatment of certain forms of paroxysmal dyspnea, and other

instances of localized or general vasoconstriction. The vasodilators, their dosage and mode of administration are as follows: amyl nitrite, 0.2 to 0.3 c.c. (3 to 5 minims) in glass ampoules that are crushed in a piece of cloth and the contents inhaled; nitroglycerin, 0.6 to 6 mgm. (1/100 to 1/10 grain), and erythrol tetranitrate, 15 to 120 mgm. (1/4 to 2 grains) in tablet form to be dissolved beneath the tongue, if they are to be immediately effective; these two drugs as well as sodium nitrite, 30 to 120 mgm. (1/2 to 2 grains) in solution, and benzyl benzoate, 0.3 to 1.3 c.c. (5 to 20 minims) in 20 per cent. alcoholic solution, have been used as more or less continuous medication without showing a constant or satisfactory effect upon hypertensive states.

Sodium thiocyanate in 0.065 to 0.3 gm. (1 to 5 grains) doses, given in solution three times a day, is at present the favorite medicinal remedy to reduce blood pressure. It is claimed that it may be given over long periods without danger of inducing toxic effects (Nichols[46]; Smith and Rudolf[47]). Gager[48] administered pure potassium sulphocyanate, 0.03 to 0.065 gm. (1/2 to 1 grain) in one teaspoonful of water, three times daily, after meals, for one week, twice daily for the second week, and once daily for the third week, and then daily or every other day; in resistant cases the more frequent dosage was maintained for several weeks; the effects on the essential hypertension are reported as excellent both as regards the lowering of blood pressure and the control of such symptoms as headache, vertigo, nervousness, etc. Dr. James Short has used this drug in our clinic and has failed to obtain convincing evidence of its value in the treatment of essential hypertension.

Mistletoe (Viscum album, Gui) has been prescribed in France and Germany for hypertensive conditions for some years' time. O'Hare and Hoyt[49] have tested this medicine, using

"Intrait de Gui", which is a 2 per cent. solution of the dry extract of mistletoe. The dose of this preparation is 2.5 to 5 c.c. (40 to 80 minims) three times a day before meals. O'Hare and Hoyt[49] continued the treatment for ten days except when the patient was relieved before that time; if no result was obtained in ten days, the drug was regarded as ineffective. They found no satisfactory reduction of blood pressure, but did succeed in relieving headache or dizziness in 75 per cent. of their cases, and tinnitus in two out of four cases. They conclude that Intrait de Gui is a useful remedy in the treatment of the more common cerebral symptoms of hypertension.

The use of iodides is a time-honored means of treating hypertension and its complications. They achieve but small results and are used very little at present. Dr. W. W. Herrick told me of one of his patients whose blood pressure would run at a distinctly lower level with very small doses of potassium iodide and rise when these were discontinued. In some cases, I believe I have obtained good results with the prolonged use of belladonna.

The failure of vasodilators and the fact that blood pressure is to a certain extent dependent upon nervous tension has led to the adoption of *sedatives* as a means of controlling hypertension. The bromides, according to O'Hare[50], "are probably the most generally useful". They may be given three times during the day with a larger dose at bedtime and are often of the greatest help. Chloral, in doses of 0.3 to 1.3 gm. (5 to 20 grains), according to the susceptibility of the patient, may be given three times during the day. A dose of 0.6 gm. (10 grains) to even 2.6 gm. or more, at night, may be of great value. During a rest cure of one or several weeks, chloral is probably more effective in reducing blood pressure and in promoting rest than

any other drug. It may not be borne well by the stomach, and in that case it can be administered advantageously in starch paste by rectum, the dose being 2.6 to 4 gm. (40 to 60 grains), once or twice a day. Chloral is a perfectly safe drug to use, though its reputation still suffers from the unwarranted belief that it is a cardiac depressant. Barbital in doses of 0.065 to 0.13 gm. (1 to 2 grains) after meals for nerve control, and in 0.3 gm. (5 grains) doses at night is very satisfactory and may be taken over long periods without any detrimental effect. Phenobarbital (Gruber, Shackelford and Eklund[51]) may be used in the same way, in doses of 15 to 60 mgm. (1/4 to 1 grain). Both barbital and phenobarbital may be combined with 0.3 gm. (5 grains) of theobromine in the daytime administration of small doses. This has been widely advocated; after considerable trial of this combination, I have been unable to convince myself that the addition of theobromine yields any results. The use of sedatives has a very distinct place in the treatment of essential hypertension, and under the circumstances it would seem wise to disregard to some extent the obvious dangers of drug addiction.

Of the *specific remedies*, liver extract (this is not the liver extract used in treating pernicious anemia) injected in from 1 to 5 c.c. doses subcutaneously once a day or at longer intervals has yielded satisfactory results in the hands of Major[52] and MacDonald[53]. Major[52] has put this preparation on a satisfactory experimental and clinical basis. However, the experience of other clinicians, who have employed this remedy, has not been entirely favorable. My patients have failed to show any drop in blood pressure with the injection of liver extract with either short intensive courses of treatment or constant treatment over a period of several years. In some of these cases the symptoms accompanying hypertension, noticeably paroxysmal dyspnea,

were relieved by its use. It remains for the future to determine exactly how valuable this remedy will prove itself in the treatment of hypertensive conditions.

There are many other special means of treatment, and good results are claimed for each one. It is more than probable that the faith of the physician in these remedies has a great effect upon the nervousness of the patient and tends to reduce the blood pressure in this way. In any event, it seems to be universal experience that an enthusiastic therapeutist is able to lower blood pressure by means that fail in the hands of the more skeptical physicians. There are numerous other remedies not of proven worth, and these will not be mentioned here.

The *treatment of the sequelae of hypertension* involves the management of cardiac disease, cerebral arteriosclerosis and nephritis. Obviously, it would lead us too far afield to take up these subjects in detail. Only a few points that have an intimate bearing on essential hypertension will be discussed.

Cardiac complications must be treated in such a way as to defer the almost inevitable dilatation and decompensation of the left ventricle. Anti-obesity diets, adequate nutrition, proper rest and sleep, exercise designed to keep the heart muscle in condition, avoidance of nervous strain, all are early precautions that anticipate this tendency. With the very first signs of cardiac decompensation digitalis is indicated in "tonic doses" and may be used over indefinite periods with benefit. It is now generally acknowledged that digitalis does not raise blood pressure, and also, that it will affect the heart action favorably, even when no irregularities exist, the pulse is slow and there is no endocarditis (Christian[54]). The management of cardiac insufficiency, of the various forms of myocardial lesions, of angina pectoris, auricular fibrillation, etc. and of valvular lesions differs

in no way from the treatment accorded these diseases of the heart in non-hypertensive states.

Cerebral arteriosclerosis is a complication of essential hypertension to which we have been able to accord only symptomatic treatment thus far. After apopleptic seizures, venesection is often resorted to with little or no effect on the blood pressure. Headaches may be nagging, may be severe, or may be so intense as to be well nigh unbearable. Their treatment has been haphazard, to say the least. A warm drink, especially coffee, may give relief; acetyl salicylic acid or other salicylates may help; sedatives may be required; the use of mistletoe has been mentioned; I have seen a few cases that were aided by quinine, and some by thyroid medication; in extreme instances, lumbar puncture has been advocated (Foster[55], O'Hare[50]). Lumbar puncture, in my experience, has been largely hit or miss in result; sometimes it is of value, at others it aggravates the condition; successive lumbar punctures in the same patient may have dissimilar effects on the headache or blood pressure.

Nephritis complicating essential hypertension is treated just as similar forms of kidney disease would be when occurring independently of a primary increased blood pressure.

Summary of Treatment. — Every case of essential hypertension should be watched closely and treated so that the blood pressure may be maintained at the lowest feasible level, and as little strain as possible put on the heart and the arteries. This is done by relief from nervous strain, proper rest and sleep, exercise so regulated that the heart, arterial and body muscles are kept in good condition and have a reserve power, diet restrictions so adjusted that obesity and erythremia are avoided but not so limited as to induce anemia or malnutrition. Drugs or physical therapy may be resorted to when necessary, but it

should be remembered that the main success of the treatment lies in the patient's confidence in the ability of his physician to help him. Complications and symptoms due to cardiac, cerebral or renal involvement must be treated as they arise.

Bibliography

1. Frost, H. M.: Hypertension and longevity, Life Insur. Med., (New England Mutual Life Insurance Co.), **1**: 178, 1926; also in Boston Med. and Surg. Jour., **193**: 241, 1925.
2. Knight, A. S.: Incidence of increased blood pressure, Proc. Assoc. Life Ins. Med. Dir. of America, **10**: 57, 1923.
3. Diehl, H. S. and Sutherland, K. H.: Systolic blood pressures in young men including a special study of those with hypertension, Arch. Int. Med., **36**: 151, 1925.
4. Fahr, G.: Hypertension heart, Am. Jour. Med. Sc., **175**: 453, 1928.
5. Rosenbloom, J.: Blood pressure studies in diabetes, Jour. Lab. and Clin. Med., **7**: 392, 1922.
6. Wiseman, J. R.: Hereditary hypertension and arteriosclerosis, Jour. Am. Med. Assoc., **78**: 409, 1922.
7. de Nador-Nikititch, E.: Sur l'etiologie de l'hypertension arterielle essentielle et de la sclérose rénale, Arch. d. Mal. du Cœur, **18**: 582, 1925.
8. O'Hare, J. P., Walker, W. G. and Vickers, M. C.: Heredity and hypertension, Jour. Am. Med. Assoc., **83**: 27, 1924.
9. Weitz, W.: Zur Ätiologie der genuinen oder vasculären Hypertension, Ztschr. f. klin. Med., **96**: 151, 1923.
10. Bordley, J., III and Baker, B. M., Jr.: Arteriosclerosis of cerebral vessels and pathogenesis of hypertension, Bull. Johns Hopkins Hospital, **38**: 20, 1926.
11. Cutler, O. I.: Relation of arteriosclerosis of the cerebral vessels to hypertension, Arch. Path., **5**: 365, 1928.
12. Major, R. H.: The possible relationship between guanidin and high blood pressure, Am. Jour. Med. Sc., **170**: 228, 1925, also, Blood chemical studies in arterial hypertension, Am. Jour. Med. Sc., **177**: 188, 1929.
13. Reid, W. D.: Arterial hypertension, Boston Med. and Surg. Jour., **192**: 883, 1925.
14. Kylin, E.: Die Hypertoniekrankheiten, J. Springer, Berlin, 1926.
15. Stieglitz, E. J.: Hypertension in pregnancy: blood calcium, Arch. Int. Med., **39**: 465, 1927.

16. Moschcowitz, E.: Pathology of hypertension, Jour. Am. Med. Assoc., **79**: 1196, 1922; Hypertension with minimal renal lesions, Jour. Am. Med. Assoc., **77**: 1075, 1921; Hypertension, its significance, relation to arteriosclerosis and nephritis and etiology, Am. Jour. Med. Sc., **158**: 668, 1919.
17. Gull, W. and Sutton, H. G.: Changes in the spinal cord and its vessels in arteriocapillary fibrosis, Trans. Path. Soc., London, **28**: 361, 1876.
18. Allbutt, C.: Diseases of the Arteries Including Angina Pectoris, Macmillan and Co., London, 1915.
19. Moschcowitz, E.: Hypertension of the pulmonary circulation, Am. Jour. Med. Sc., **174**: 388, 1927.
20. Pal, J.: Über Herzhypertrophie und Hypertonie, Med. Klinik, **15**: 662, 1919.
21. Moschcowitz, E.: Congenital peripheral resistance; its causal relation to the hypertensive states, Arch. Int. Med., **33**: 566, 1924..
22. Bell, E. T. and Clawson, B. J.: Primary (essential) hypertension: a study of four hundred and twenty cases, Arch. Path., **5**: 939, 1928.
23. Monakow, P.: Blutdrucksteigerung und Mere, Deutsches Arch. f. klin. Med., **133**: 129, 1920.
24. Fishberg, A. M.: Anatomic findings in essential hypertension, Arch. Int. Med., **35**: 650, 1925.
25. O'Hare, J. P. and Walker, W. G.: Arteriosclerosis and hypertension, Arch. Int. Med., **33**: 343, 1924.
26. Lange, F. and Wehner, E.: Das Herz bei Hypertonie und bei Arteriosclerose, Deutsch. Arch. f. klin. Med., **160**: 45, 1928.
27. Aschoff, L. and Tawara, S.: Die Heutige Lehre von den Pathologischanatomischen Grundlagen der Herzschwäche, Gustave Fischer in Jena., 1906.
28. Clawson, B. J.: The myocardium in non-infectious myocardial failure, Am. Jour. Med. Sc., **168**: 648, 1924.
29. Allan, G.: Diseases of the coronary arteries, Brit. Med. Jour., **2**: 232, 1928.
30. Janeway, T. C.: The Clinical Study of Blood Pressure, D. Appleton & Co., New York, 1904.
31. Pal, J.: Gefässkrisen, Leipzig, 1905.
32. Boas, E. P. and Fineberg, M. H.: Hypertension in its relationship to mitral stenosis and aortic insufficiency, Am. Jour. Med. Sc., **172**: 648, 1926.
33. Levine, S. A. and Fulton, M. N.: Relation of hypertension to mitral stenosis, Am. Jour. Med. Sc., **176**: 465, 1928.

34. O'Hare, J. P. and Walker, W. G.: Arteriosclerosis and hypertension, Arch. Int. Med., **33**: 343, 1924.
35. Cohen, M.: The value of ophthalmoscopic signs in the pre-apoplectic stage, Psychiatic Quart., **2**: 59, 1928.
36. Keith, N. M., Wagener, H. P. and Kernohan, J. W.: The syndrome of malignant hypertension, Arch. Int. Med., **41**: 141, 1928.
37. Philipps, J.: Discussion, Am. Heart Jour., **1**: 652, 1926.
38. Paullin, J. E.: Results of essential hypertension, Jour. Am. Med. Assoc., **87**: 925, 1926.
39. Willius, F. A.: Electrocardiography and prognosis, Arch. Int. Med., **30**: 434, 1922, also, Clinical and pathologic data in cases exhibiting T wave negativity in the electrocardiograms, Am. Jour. Med. Sc., **175**: 630, 1928.
40. Pardee, H. E.: Heart disease and abnormal electrocardiograms, with special reference to the coronary T wave, Am. Jour. Med. Sc., **169**: 270, 1925.
41. Horine, E. F.: Prognosis in rheumatic, hypertensive and syphilitic heart disease, Am. Heart Jour., **1**: 617, 1926.
42. Hepburn J. and Jamieson, R. A.: The prognostic significance of several common electrocardiographic anomalies, Am. Heart Jour., **1**: 623, 1926.
43. Christian, H. A.: Discussion, Jour. Am. Med. Assoc., **87**: 931, 1926.
44. Elliott, A. R.: Essential hypertension, Am. Jour. Med. Sc., **174**: 244, 1927.
45. Rappaport, I.: Blood pressure and respiration, Jour. Am. Med. Assoc., **92**: 1158, 1929.
46. Nichols, J. B.: Discussion, Jour. Am. Med. Assoc., **87**: 930, 1926.
47. Smith, A. G. and Rudolf, R. D.: Use of sulphocyanate of soda in high blood pressure, Canad. Med. Assoc. Jour., **19**: 288, 1928.
48. Gager, L. T.: The incidence and management of hypertension, Jour. Am. Med. Assoc., **90**: 82, 1928.
49. O'Hare, J. P. and Hoyt, L. H.: Mistletoe in treatment of hypertension, New England Jour. Med., **199**: 1207, 1928.
50. O'Hare, J. P.: Treatment of hypertension, Am. Heart Jour., **2**: 510, 1927.
51. Gruber, C. M., Schackelford, H. H. and Ecklund, A. M.: The effect of phenobarbital on blood pressure in arterial hypertension, Arch. Int. Med., **26**: 366, 1925.
52. Major, R. H.: The effects of hepatic extract on high blood pressure, Jour. Am. Med. Assoc., **85**: 251, 1925.
53. MacDonald, W. J.: Extractives of liver possessing blood pressure

reducing properties. Report of clinical tests, Proc. Soc. Exper. Biol. and Med., **22**: 483, 1925.

54. Christian, H. A.: Digitalis effects in chronic cardiac cases with regular rhythm in contrast to auricular fibrillation, Med. Clin. North Am., **5**: 1173, 1922.

55. Foster, N. B.: Treatment of hypertension, Jour. Am. Med. Assoc., **79**: 1089, 1922.

CHAPTER X

CLINICAL CONCEPTION OF NEPHRITIS — BRIGHT'S DISEASE

Introduction

Nephritis, or Bright's Disease, is a group of maladies in which certain non-suppurative lesions of the kidney are present. These affections differ widely from each other in regard to morphological, as well as functional, pathology.

For the clinician, the greatest help in diagnosis and guidance to treatment is obtained when every case is analyzed so that the following six points are considered independently:

Pathology of the Kidney and other Tissues
Renal Function
Edema
Blood Pressure
Anæmia
Uræmia

Clinical Conception of Nephritis — Bright's Disease

The study of nephritis thus far has failed to crystallize our conception of it into a clear-cut clinical entity; hence we are unable to think of it as a malady that may be traced from initial etiology, through symptoms and signs, paralleled by definite pathological lesions. The confusion of our ideas is perhaps greater today than it was twenty years ago, when the very simple, but what now seems naïve, thought dominated

the situation, that a non-suppurative disease of the kidney besides giving evidence of its local irritation in the urine (albumin, casts, red blood cells) characterizes the disease nephritis through diminishing renal activity and consequent retention of the urinary excretory products by a definite train of symptoms, which may be epitomized as edema, uræmia and hypertension.

It is now recognized that edema may be present or remain in abeyance during acute nephritis, that edema is not necessarily directly proportional to the degree of oliguria, as in bichloride of mercury poisoning, that uræmia may occur without an increase in the blood urea nitrogen, that hypertension and "albuminuric retinitis" may be found in patients whose kidneys are normal. These and many similar facts lead to the inevitable conclusion that, what we describe today as nephritis, is not a disease localized in the kidneys with secondary manifestations elsewhere, but is a constitutional disorder whose many-sided aspects we are only beginning to appreciate. The revival of interest in liver pathology in nephritis and the surprising and growing importance of the thyroid gland in the study of cases of nephrosis point in this direction.

The concept of nephritis originated with Richard Bright's[1] world-renowned papers, published between 1827 and 1843. He was the first to point out the concurrence of renal disease, albuminuria, edema and cardiac hypertrophy (implying high blood pressure). In the following years attention was focused mainly upon the anatomical changes in the kidney; Traube succeeded in demonstrating passive congestion and amyloid disease of the kidney as apart from nephritis; G. Johnson formulated the dual character of Bright's disease, noting that the lesions of nephritis might originate either as an inflammatory process or as an arteriosclerosis; Friedrich Müller[2] dif-

ferentiated between the primary glomerular, inflammatory changes in the kidney and the primary tubular, degenerative lesions which he termed nephrosis.

Meanwhile the study of kidney function did not progress until the phenolsulphonephthalein (the "dye", the "red" or the "P.S.P.") test of Rowntree and Geraghty[3] (1912) became available. This procedure was supplemented shortly by the micro-blood chemical methods of Folin and the urinary specific gravity determinations of Schlayer. The investigation of nephritis from the two viewpoints, the anatomical and the functional, revealed the very significant fact that anatomical lesions and impairment of renal function very frequently do not run parallel.

Bright in his publications states definitely that he was not certain whether he was describing several diseases or progressive stages of the same condition. In 1871 Grainger spoke of "Bright's diseases"; Addis[4] (1925) does the same, believing that in the concept of nephritis there are included "—three diseases which are pathologically and etiologically distinct and separate". There can be no doubt that several widely divergent conditions associated with one another only through the localization of various pathological lesions within the kidneys have been placed in the category of nephritis or Bright's disease. The definition which considers the kidney lesions as the pivotal point in the situation is very well given by Christian and O'Hare[5]: "Nephritis may be defined as a diffuse, progressive, degenerative or proliferative lesion involving the renal parenchyma, the interstitial tissue or the renal vascular system". They add, that these lesions are non-suppurative, and that by diffuse they mean a wide distribution of the lesions in both kidneys though the involvement may be either focal or

uniform. Many authorities believe that only inflammatory changes should be designated as nephritis, that the tubular degenerative lesions should be called nephrosis and the vascular degenerative disease be thought of as vascular nephropathy or nephrosclerosis.

That era in the study of nephritis, when the goal of the clinician was a correct anatomical diagnosis of the gross and microscopic lesions of the kidney, has passed, although with a clearer realization of our limitations, this can be done with greater accuracy and more confidence now than formerly. Uræmia, acidosis, alkalosis, hypoglycæmia, etc., may cause death in the absence of lesions from which the pathologist can draw conclusions. At present the diagnosis of hypertension at post-mortem examination usually is based on the existence of cardiac hypertrophy, which is a sequel to a high blood pressure and not its cause. In other words, such diagnoses can be made accurately only on the living subject.

The so-called symptoms of nephritis do not always follow upon the lesions in the kidney, but are, to a large extent, independent processes brought about by the same etiological agent as the nephritis. To think of typhoid fever as enteritis is comparable to considering Bright's disease as "nephritis". It would be better to regard the kidney lesions as part of an arteriosclerosis, or the result of infection by the hemolytic streptococcus. However, such an etiological nomenclature is impossible at the present time, since our knowledge of the causation of the various forms of nephritis is unsatisfactory. Taking these and other facts into consideration, it would seem wise to speak of "nephritis" as Bright's disease, and in so doing honor the man who first formulated the conception that albuminuria, kidney lesions, edema and hypertension were

linked together in a clinical entity. Furthermore, it is especially desired to stress the fact that this is not Bright's renal disease, but is Bright's disease, a group of maladies in which the kidney assumes no greater importance than other factors which, like the changes in the kidney itself, are being clarified at the present time.

Attempts at a classification of Bright's disease, based on the conception of a primary renal lesion inducing certain sequelæ are not convincing. In most treatises on this subject, the independence of kidney pathology and symptoms is granted, but generally the point is not carried out consistently, and the whole exposition of Bright's disease usually is grouped about the various forms of nephritis and nephrosis. Theodore Janeway[6], in a Harvey lecture, in 1913 expressed the idea that in functional pathology Bright's disease presents the aspect of a three-fold problem, edema, uræmia and hypertension. I believe that at the present time we may add renal function, renal pathology and anæmia, and thus complete the list of problems in regard to both functional and morphological pathology that demand elucidation in every case of Bright's disease. Since these various phases do not proceed apace in any nephritic subject, it is necessary to analyze the factors in each patient and to consider them separately. The results of such a clinical analysis, or diagnosis, are much more satisfactory than the attempt to pigeonhole a case as "acute nephritis", "secondary contracted kidney", etc., terms of great latitude in their clinical significance. The indications for treatment also are clarified in this way as well. For some time we have been making an analysis and diagnosis of our cases of Bright's disease in this fashion, and the procedure has proved to be very helpful. An example is the following:

Problem. — Treatment of albuminuria.

History. — D. G., schoolboy, age 18. Past history is negative except that there was a pneumococcus conjunctivitis on two occasions, two years ago and again five months ago. The tonsils have been removed on two occasions; the sinuses have been examined and are negative. Six weeks ago there was an edema of the ankles; the urine was examined, and a marked amount of albumin demonstrated.

Physical Examination. — Normal height and normal weight for age. Well nourished. The mucous membranes are rather pale and slightly cyanotic. Teeth are in good condition. The tonsils have been removed successfully. Pulse rate is 96; the pulse is regular. Blood pressure is 138/88. The heart shows some enlargement to the left and downward. The precordial dullness is $1\frac{1}{2} \times 14$ cm. with the apex in the 6th space. The aortic second sound is louder than the pulmonic second sound but is not unduly accentuated; there are no murmurs. The edge of the liver extends two finger breadths below the costal margin. There is no edema of the ankles or elsewhere. In other respects, there is nothing of note in the physical examination.

Blood Count:	Hæmoglobin	75%
	Red Blood Cells	5,192,000
	White Blood Cells	7,500
	Differential Count:	
	Polymorph.	73%
	Small mon.	14%
	Large mon.	1%
	Eosinoph.	4%
	Basoph.	0
	Trans.	1%
Blood Chemistry:	Urea N	23.7 mg. per 100 c.c.
	Uric acid	3.9 mg. per 100 c.c.
	Cholesterol	246 mg. per 100 c.c.

Routine Urine Analysis: Specific gravity 1.012; reaction acid; albumin, marked

reaction; sugar none; indican, marked trace; diacetic acid none; microscopic, many white blood cells, a few red blood cells, a few coarse granular and occasional hyaline casts. Albumin in the day specimen is 3 grams per liter and in the night specimen is 2 grams per liter.

Two Hour Test for Renal Function: while on usual diet.

Time	Volume c.c.	Sp. Gr.	NaCl		Urea	
			%	gms.	%	gms.
8.00–10.00	110	1.012				
10.00–12.00	170	1.012				
12.00– 2.00	140	1.015				
2.00– 4.00	170	1.015				
4.00– 7.00	200	1.016				
7.00–10.00	250	1.016				
Total day	1040		0.7	7.3	1.2	12.5
Total night	670	1.012	0.66	4.4	1.0	6.7
Total	1710			11.7		19.2

Clinical Impression. — Renal Pathology: The albuminuria has been present for six weeks at least; it may have been present for a considerably longer time; it is impossible to be certain of this since an acute nephritis may not exhibit any edema at its onset; six weeks ago, there was a little edema, and consequently it may be concluded either that there was an onset of an acute nephritis at that time or an acute exacerbation of a chronic nephritis. The blood pressure is slightly elevated; there are coarse, granular casts and a few red blood cells in the urine; all of which point to the existence of either acute or chronic nephritis. The fact that the heart is somewhat hypertrophied and considerably dilated would indicate that the hypertension is of more than six weeks' duration, and therefore the condition, in all probability, may be considered as a chronic nephritis with an acute exacerbation beginning six weeks before. The increase in the blood cholesterol may be indicative of a certain degree of tubular degeneration (nephrotic element).

Renal Function: The kidney function is somewhat impaired, as shown by the slight increase in the blood urea nitrogen and the blood uric acid. In the two-hour test for renal function, the specific gravity does not reach the level of 1.020, nor is the variation of specific gravity between the lowest and the highest reading in the two-hour test more than 4. This does not represent a maximal impairment of renal function but one of moderate degree. During an active acute nephritis there is oliguria and a high fixed specific gravity (at a level of 1.020 or greater), neither of which hold true here. In acute nephritis, during the stage when edema is being eliminated and subsequently, the specific gravity is lower, fixed at times, variable at others, depending upon the volume of urine. This would cover the situation in the present instance. However, if this were correct, the blood urea nitrogen would be at a normal level and not in the least elevated (23.7 mg. per 100 c.c. of blood in this patient), since in the polyuric stage of an acute nephritis it is rare to find a urea retention. Consequently, the interpretation of the present tests for renal function would point to a chronic nephritis, with a destruction of a considerable number of the glomeruli, thus confirming the conclusion made under the heading of renal pathology.

Edema: The edema was slight six weeks ago, indicating an acute exacerbation of a chronic nephritis at that time. There is no edema at the present moment.

Blood Pressure: This is moderately but distinctly increased. In view of the history of the case, the moderate increase in the arterial tension and the presence of a marked albuminuria, indicating an inflammatory nephritis, the rise in blood pressure probably is secondary to the nephritis and is not a primary or essential hypertension. At the present time, the blood pressure

is not elevated enough to demand treatment, although it may have been higher in the past and played a rôle in causing the cardiac hypertrophy and dilatation; there are some indications that the heart is not compensating perfectly such as slight cyanosis, a rather rapid pulse rate, dilatation of the left ventricle, enlargement of the liver and a high red blood cell count with a comparatively low hemoglobin content.

Secondary Anæmia: This is slight, which would confirm the idea that there is only a moderate degree of impairment of renal function.

Uræmia: There are no signs of uræmia.

Diagnostic Summary. — Acute exacerbation of a chronic nephritis; the acute exacerbation has been slight and has largely run its course; there is a considerable albuminuria, a moderate hypertension, with a slight degree of cardiac decompensation, a moderate impairment of renal function, a slight secondary anæmia, no edema and no uræmia.

Treatment. — From this analysis, it may be readily concluded that, at the present moment, the only factor which requires attention is the inflammatory and degenerative processes going on in the kidney. The other phases of this case of Bright's disease are absent or in abeyance and thus of minor importance. However, they must be watched for, especially cardiac failure (secondary to hypertension) and renal insufficiency, of which the premonitory signs have been noted. Because of the rather high polynuclear percentage, close scrutiny should be exercised to determine whether any foci of infection have escaped observation and proper treatment accorded them if found. The patient should be made to understand the grave risk of any acute infection, however mild, since this always brings with it the danger of an exacerbation of the nephritis.

The analysis of the above case illustrates how, by an investigation directed towards ferreting out the significance of the major problems in Bright's disease, clearer indications are obtained for the treatment of the individual than if the patient is considered simply as a case of chronic nephritis, and the routine procedure applicable to chronic nephritis is plunged into indiscriminately.

Believing that Bright's disease is really composed of several processes that develop more or less independently, and to different degrees in various patients, these "problems in Bright's disease" will be taken up in separate chapters and treated as entities, but with due consideration of their relation to other phases of the subject. The concept of Bright's disease will be discussed and analyzed under six headings:

1. Pathology of the Kidney and other Tissues.
2. Renal Function.
3. Edema.
4. Blood Pressure.
5. Anæmia.
6. Uræmia.

Whenever indicated, classifications will be attempted. Classifications give a false sense of security in fostering the idea of completely acquired knowledge; in this respect, they are dangerous. However, a classification is a necessary starting point from which to reason; it is misleading to accept it as a final guide to diagnosis and treatment for, as Senator, one of the greatest students of kidney diseases, says: "All classifications are more or less artificial, though for the sake of orientation and teaching they may be necessary; they can never be completely satisfactory because of the many transitional and combination forms that are always found."

Bibliography

1. Bright, R.: Reports of Medical Cases, London, Longman, Rees, Orme, Brown and Green, **1**: 67, 1827. Cases and Observations Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, Guy's Hospital Report, **1**: 338, London, 1836.
2. Müller, F.: Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch., 64, 1905.
3. Rowntree, L. G. and Geraghty, J. T.: The phthalein test, Arch. Int. Med., **9**: 284, 1912.
4. Addis, T.: A clinical classification of Bright's disease, Jour. Am. Med. Assoc., **85**: 163, 1925.
5. Christian, H. A. and O'Hare, J. P.: Nephritis, The Oxford Medicine, Oxford Univ. Press, Am. Branch, **3**: 583, New York, 1924.
6. Janeway, T. C.: Nephritic hypertension: clinical and experimental studies, Am. Jour. Med. Sc., **145**: 625, 1913.

CHAPTER XI

PATHOLOGY OF THE KIDNEY AND OTHER TISSUES IN BRIGHT'S DISEASE

(Description, Signs, Symptoms, Diagnosis and Treatment of the Pathological Lesions of Bright's Disease)

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In describing the pathology of Bright's disease it has been customary to consider only the anatomical changes in the kidneys. The occurrence of protein, red blood cells and casts in the urine is linked so closely with the renal lesions that it clarifies the morphological diagnosis to think of them together. Therefore, these subjects have been included in this chapter. Furthermore, if the various forms of Bright's disease are constitutional affections, as most of us believe, rather than conditions whose sole pathology is found in the kidneys, it is only logical to discuss here the changes in the retina and elsewhere. Our knowledge of the extra-renal pathology in Bright's disease is still very meagre, but its development promises much in the future

Albuminuria

By albuminuria is meant the presence of any protein material, not only albumin, in the urine. Besides albumin, globulin and other proteins as well are found in the urine. The name proteinuria would be more appropriate, and this term is used in some clinics, but time-honored habit calls for the use of the word "albuminuria". A normal urine is considered usually to be protein-free, indicating that the glomerular capillaries are impervious to the serum proteins. There is a small amount of protein material in normal urine. This is so slight that on layering the urine over cold nitric acid (Heller's test) there is a negative result; on the other hand, the heat and acetic acid test, when properly carried out, frequently will show a slight

quantity, technically designated as the faintest possible trace. The inexperienced clinical pathologist often has difficulty in placing such traces in their proper category. The ordinary wear and tear of the lining membranes of the urinary tract probably is the source of such slight traces of protein.

Sources of Albuminuria. — For the clinician two main types of albuminuria may be distinguished, those arising in the kidneys and those whose origin may be traced to other parts of the genito-urinary tract. Any condition, that can give rise to pus or blood in the urine, such as cystitis, vaginitis, urethritis, calculus, etc., may be responsible for an albuminuria. Sometimes these conditions are distinguished easily from a renal involvement incident to Bright's disease, passive congestion, polycystic kidneys, etc., but at other times it is most difficult to do so. The presence of casts in the urine indicates that the renal parenchyma is involved; however, this is not pathognomonic, as urinary tract disease often is associated with a slight renal irritation not deserving particular consideration.

The Elimination of Protein by the Kidney. — The usual proteins of the blood do not pass through the normal kidneys into the urine in appreciable quantities. When albuminuria exists because of elimination of protein by the kidney, the site of excretion of the protein is believed to be in the glomeruli and not in the tubules (Cushny[1], page 241). Two reasons usually are given for the passage of proteins through the kidney. These are (1) damage of the glomerular capillaries, (2) the presence of abnormal proteins in the circulation.

Damage of the glomerular capillaries resulting in albuminuria may be brought about in several ways. Of these, passive congestion and inflammation are the most important. The albuminuria incident to tubular degenerations (nephrosis) will

be discussed a little further on. What the lesion of the glomerular capillaries in these conditions is, remains an open question. The most favored view is that the congestion or inflammation renders these capillaries more permeable; the smaller albumin molecule in larger quantities and the larger globulin molecule in smaller amounts thus are allowed to escape into the urine.

The presence of foreign proteins in the circulation results in their prompt elimination in the urine. This is true, whether these proteins are formed within the body (e.g., Bence-Jones proteinuria, hemoglobinuria) or are derived by absorption or injection. Andrews, Thomas and Welker[2] believe that albuminuria "is due to alteration of normal serum proteins by their combination with other split protein products which render them foreign to the circulation". Albuminuria thus would be "a detoxicating mechanism for eliminating poisonous products of protein metabolism". Another, somewhat similar, statement regarding the origin of urinary proteins is made by Andrews and Thomas[3]: "It is probable that nephritis is not a renal disease but a disturbance of the mineral metabolism causing a disintegration of the great parenchymatous organs, which allows the proteins to leak into the blood and pass through the kidneys as foreign proteins. By some unknown mechanism, this process, once initiated, is likely to continue and involve the leakage of blood proteins as well." These views are exceedingly interesting and are well worth bearing in mind, though they have not been developed sufficiently to be of clinical importance.

The albuminuria of tubular degenerative renal disease (*nephrosis*) obviously is not explained satisfactorily on the basis of a glomerular lesion that is assumed to be the cause of elimination of protein in Bright's disease. Degeneration, destruction and

loss of the cells lining the renal tubules may give rise to a certain degree of proteinuria but cannot be the source of the very large amounts of protein found in typical active cases of nephrosis. The suggestion has been made, though not generally accepted, that the tubular wall denuded of its cellular lining exposes the underlying capillaries allowing the proteins to pass readily into the tubular lumen. Epstein[4] has made a number of studies in which he concludes that nephrosis is not primarily a renal disorder, but a constitutional disturbance in which the extra-renal factors are of prime importance. According to him, the serum proteins are changed in some way in nephrosis and thus promptly eliminated by the kidney. Pointing out the analogy of the excretion of such a surplus of protein to the elimination of sugar in diabetes mellitus, Epstein gives the name of *diabetes albuminuricus* to nephrosis.

The albumin: globulin ratio may be determined in the urine. This has a certain diagnostic and prognostic significance in Bright's disease. Hiller, McIntosh and Van Slyke[5] summarize their findings on this point as follows: "The albumin: globulin ratio of the urine proteins was found usually above 10 in nephrosis; between 5 and 10 in acute nephritis, with a low ratio during the early stage followed by a higher ratio during recovery; usually below 5 in the advanced stages of chronic glomerular nephritis with urea retention and impaired kidney function. In one case of amyloid nephrosis the ratio was very low, 1.5, in accord with the previous literature.

"The low ratios in advanced chronic nephritis were associated with low urea concentration indices and poor prognoses. Of 15 cases observed with average urinary albumin: globulin ratios below 5, all but 2 have died in less than 18 months, and these 2 have shown progressive decrease in renal function."

The quantity of protein eliminated in the urine varies a great deal; there may be mere traces or the amounts may be extremely large. Epstein[4], in a case of nephrosis, observed an albuminuria of several months' duration with a daily output of protein ranging from 18.5 to 26.2 grams. There are several points of practical importance to be noted in interpreting the significance of the amount of protein substance in the urine: the daily fluctuations in chronic Bright's disease are of comparatively little significance; in acute Bright's disease a healing of the inflammatory process is accompanied by a diminution and a disappearance of the albuminuria; the degree of albuminuria is not an indication of the degree of impairment of renal function but is a sign of the type of Bright's disease which prevails; in acute and chronic glomerular nephritis and in nephrosis the albuminuria is marked, but in sclerotic disease, associated with arteriosclerosis, usually it is slight and even may be absent, although the kidney may be extensively involved and its excretory power reduced to the vanishing point.

Various forms of albuminuria have been demonstrated. Their relation to the albuminuria of Bright's disease is not understood thoroughly, and frequently it is very difficult to be certain whether the protein found in the urine is significant of a lesion in the kidneys or not. The so-called *physiologic albuminurias*, which apparently occur in most normal individuals after severe, or even moderate, physical and mental effort and frequently after cold baths, are well known; the medical director of a life insurance company tells me that the prevalent Sunday automobile excursion commonly is productive of albuminuria on Mondays. Such transient traces of protein in the urine apparently are almost universal and are of no pathological significance.

Orthostatic albuminuria is an albuminuria which occurs only while an individual is in the upright position, disappearing when he lies down. Heubner[6] definitely established the fact that this phenomenon could occur in a person whose kidneys were normal; he demonstrated this by autopsy findings on a patient with orthostatic albuminuria, who succumbed to another disease. Jehle[7] has shown that some of these cases are the accompaniment of a marked lordosis. Erlanger and Hooker[8] demonstrated that a lower pulse pressure on standing might be a cause. Undoubtedly many individual factors may contribute to this condition. The most important fact for the clinician to bear in mind is that no matter how clear the indications may seem to be, whether casts or other signs of Bright's disease are present or not, it is often impossible to be certain that such a case is a benign form of albuminuria, that is, one not associated with any renal pathology. Many cases of Bright's disease exhibit what might be called an orthostatic type of albuminuria, though this may be regarded as a good prognostic sign and often accompanies a healing kidney lesion in Bright's disease.

An *epidemic of albuminuria* is described by Ashburn[9] in a very interesting report. He notes: "Albuminuria may occur in healthy men without being significant of serious kidney disease. Occasionally, as in 1925 and in 1926 at West Point, this condition may attain epidemic prevalence." Most of Ashburn's cases were of short duration, though some lasted six months to a year or more.

The effects of albuminuria may be far reaching, "for it is calculated that as much as one-tenth to one-fifth of the total protein of the plasma may be lost each day in severe cases" (Cushny[1], page 246). The loss of a large amount of protein may be responsible for a *secondary anæmia* (Ashe[10]). In 1836

Bright noted the presence of an excess of fat and a diminished protein content of the blood in cases exhibiting edema and albuminuria. These findings have been confirmed in many quarters and have been emphasized especially by Epstein[4]. In cases of chronic nephrosis with marked, prolonged albuminuria, the total protein of the blood serum diminishes. This is due mainly to a loss of albumin content, while the globulin may increase or remain practically unchanged. *The low total serum protein and the depressed albumin: globulin ratio are characteristic of chronic nephrosis with marked albuminuria* (table 31). Linder, Lundsgaard and Van Slyke[11] confirm these observations

Average Composition of Blood Sera. Grams per 100 c.c.

	Total Protein	Globulin	Albumin	Ratio of albumin to globulin
Normal.....	7.400	2.738	4.662	1.702
Cardiac conditions..	6.408	2.240	4.417	1.971
Nephrosclerosis....	6.704	2.396	4.310	1.790
Chronic nephrosis..	3.928	3.462	0.466	0.131

Table 31. — In chronic nephrosis the total protein, the albumin and the albumin: globulin ratio are very low, while the globulin remains comparatively unchanged or may be increased (Epstein[4]).

and note that such changes run directly proportional to the proteinuria, and that when the albuminuria becomes slight or ceases, the blood serum proteins return to normal. They add that, in addition to the loss of protein in the urine, there probably occurs a disturbance in the production of the plasma proteins.

The milky and opaque serum observed by Bright in 1836 is substantiated by the *high cholesterol values in cases of chronic nephrosis*. Table 32, taken from Epstein's[4] work, shows this very well. The cause for such a cholesterinemia remains un-

CHOLESTERIN CONTENT OF BLOOD SERA. MILLIGRAMS PER 100 C.C.

Diagnosis	Cases	Average	High	Low
Nephrosclerosis....	24	174	265	100
Uræmia.....	5	133	194	87
Arteriosclerosis.....	7	163	218	100
Cardiac conditions..	19	157	294	104
Bichloride poisoning	2	127	130	125
Chronic nephrosis..	9	559	1230	333

TABLE 32. — The cholesterol of the blood may be very much increased in cases of chronic nephrosis but is normal in other renal diseases and in cardiac conditions (Epstein[4]).

explained. To say that it is a sign of malnutrition or a disturbance in the proper assimilation of lipoids or a metabolic disorder, does not clarify the situation greatly. The finding of Hiller, Linder, Lundsgaard and Van Slyke[12] that patients with a marked cholesterinemia were able to burn fat as efficiently as normal individuals serves to limit the speculative field considerably. Thus, for the present, the demonstration of an increase in the blood cholesterol has a diagnostic value only. It serves to point to the existence of a constitutional disturbance that often is associated with tubular degenerative renal lesions that are called nephrosis.

URINARY CASTS

Urinary casts are microscopic structures that are molds or "casts" of the tubules. They are usually, but not invariably, associated with albuminuria. A few casts of the hyaline variety may occur in the urine which is, clinically speaking, free from albumin. "Very often the protein solution is solidified in the tubules, by the absorption of the water together with the increasing acidity, and a 'cast' of the tubule is formed and is finally driven downwards by the pressure from behind and

appears in the urine" (Cushny[1], page 244). It is best to examine fresh samples of urine for casts as they are prone to be dissolved on standing; this is especially true of dilute or alkaline specimens (Addis[13]).

Hyaline casts are the most frequent. They are clear, homogeneous structures with rounded ends and presumably represent the matrix from which all other varieties of casts are formed. Hyaline casts may occur at times, particularly after physical effort, in the urine of all normal persons, just as do traces of albumin. They are the characteristic finding in cases of pure arteriosclerotic disease of the kidney (nephrosclerosis). Hyaline casts furnish the material to which the cellular elements and detritus of the glomeruli and tubules, incident to inflammatory or degenerative processes, may adhere or in which they may become imbedded. Consequently there are *finely granular casts*, *coarsely granular casts*, *blood casts*, *epithelial cell casts*, *pus casts and fatty casts*.

The names of these casts are sufficiently descriptive to indicate both their appearance and significance. Blood casts have been considered pathognomonic of glomerular nephritis, especially during the acute stage of this condition (Addis[13]). Fatty casts may contain only a few droplets of fat or may be composed almost entirely of fat globules. The origin of this fat is presumably from degenerated epithelial cells. In cases of "lipoid nephrosis" double refractile lipoids have been found in the urine and imbedded in the casts. Markedly fatty casts, or lipoidal casts, are not found very commonly. *Waxy* casts are wider, longer, composed of denser material and consequently have a sharper outline than hyaline casts. Their composition is unknown. Formerly they were thought characteristic of amyloid disease, but this idea has been discarded. Waxy

casts are found principally in cases of chronic nephritis in which there is a very severe degenerative process of the kidneys.

"*Renal failure casts*" (uræmic casts) have been described by Addis[14]. These are distinguished by their unusual breadth; they are formed in the collecting tubules; they are found most usually in cases of nephritis associated with marked renal insufficiency and impending true uræmia, though they may be present in mercury poisoning and in generalized bacterial infections. These casts may be cellular, or homogeneous, resembling waxy casts except for their greater width, or coarsely granular. The last is by far the most common variety. However, all these forms originate as cellular casts. Addis believes that these casts are present in the urine of every case of true uræmia, that is, uræmia brought on by renal insufficiency.

Cylindroids are structures that resemble hyaline casts but differ from them in that their ends are pointed instead of being rounded. They are probably of the same importance as hyaline casts though many believe that they have no pathological significance.

Hematuria

A few red blood cells can be found in all urines, if a sufficient quantity is centrifuged. Consequently, an occasional red blood cell in the urinary sediment is of no great significance. A large number of red blood cells in the urine usually is considered to point to calculi, carcinoma, tuberculosis or acute inflammatory conditions of the urinary tract. Such conditions often are confused with the hematuria that occurs in Bright's disease. The red blood cells in the urine may have the typical biconcave appearance with a reddish color throughout their substance, such as they present within the blood stream. On

the other hand, the red cells may become distorted, colorless, swollen and appear as spherical structures of which the outline only is visible. It is exceedingly difficult, under these circumstances, to distinguish between red blood cells and yeast cells. It is advisable, in carrying out the microscopic examination of the urine, to bear in mind that these elements can be distinguished from one another only by careful study with a high-power and not with a low-power lens.

Hematuria in Various Types of Nephritis

Glomerular nephritis is the type of renal lesion in Bright's disease that is especially characterized by the appearance of blood in the urine. This is so distinctive of this form of kidney lesion that Addis[13] has termed it the "hemorrhagic" variety. One of the most common initial symptoms of acute glomerular nephritis is the appearance of blood in the urine. When this is marked, the urine assumes a claret color; with less blood it is mahogany brown or may even be only blood tinged. In some cases of acute glomerular nephritis, the blood may be so small in amount in the urine as to be visible with a microscope only. These cases may escape detection entirely, unless the occurrence of edema furnishes a clue. When the amount of blood in the urine is large, blood casts may occur. These casts, as previously mentioned, are pathognomonic of glomerular nephritis, whether acute or chronic. With the subsidence of the inflammatory process in the kidney, the hematuria has a tendency to diminish, and the urine may assume a characteristic, grayish tinge, which has been designated as "smoky". It should be remembered that, since the glomeruli are the source of the blood in the urine, a lessening of the hematuria may have a double interpretation. In the first place, usually it is con-

sidered as indicating a slowing of the inflammatory process and thus regarded as a good prognostic sign; in the second place, however, a disappearance of the red blood cells in the urine may point to a cessation of the circulation within the glomerular capillaries which, of course, is not a favorable omen. This may be brought about in one of two ways; either by the proliferation of epithelium within Bowman's capsule, that is, the formation of epithelial crescents, and the consequent compression of the glomerular tuft, or it may be the result of the obstruction of the blood flow due to the accumulation of inflammatory products within the walls of the capillaries. In either event, the diminution or disappearance of hematuria under these circumstances would point to an advancing pathological process within the kidney and not a receding one. In those cases in which the glomerular circulation is re-established, the walls of the glomerular capillaries may be torn and hematuria again become evident. Fahr[15] (page 302) calls attention to these facts, saying that they have been pointed out previously. (Rochs quoted by Christian and O'Hare, Oxford Medicine, Vol. 3: 669.) I do not believe that they are known generally. During the chronic stage of glomerular nephritis, red blood cells and blood casts may persist in the urine, or they may disappear. These elements certainly reappear with every acute exacerbation of glomerular nephritis, and their presence in a urine, that previously has been free from them, furnishes the best criterion by which the inflammatory involvement of the kidney may be judged. In the terminal stage of a glomerular nephritis, that is, the stage when connective tissue replaces much of the renal parenchyma (secondary contracted kidney), the blood cells are prone to disappear from the urine entirely.

Tubular nephritis (*nephrosis*) is believed to be characterized

by an absence of red blood cells in the urine. When these do occur, it is believed to be a sign that the glomeruli are involved. It must be recognized that there are very few cases of nephritis, in which the lesion is purely tubular or purely glomerular, and there need be no question but that there is glomerular involvement, when red blood cells are found in the urine of a patient, who presents all the signs and symptoms characteristic of a tubular kidney lesion.

In *arteriosclerotic nephritis* red blood cells are absent in the urine. This is to be expected, since the circulation in the glomerular capillaries must diminish as the renal arterioles become sclerosed. When heart failure brings about passive congestion in such kidneys, red blood cells may occur in small or moderate numbers in the urine. In the necrotizing form of this disease, which sometimes comes on as a terminal event in cases with a very high diastolic blood pressure, hematuria does occur. Occasionally hypertensive patients have a hematuria that can be ascribed only to the bursting of a large or small vessel within the kidney as the result of the continued strain of a persistently high blood pressure.

Pathology of the Kidney in Bright's Disease — Nephritis

A description of the pathological lesions of the kidney has been used habitually as a basis for the classification of Bright's disease. This is the thought that is carried through by Volhard and Fahr[16] and subscribed to in the publications of Elwyn[17] and of Fishberg[18]. Other criteria have been added by Delafield and more recently by Christian[19], who used edema (which may possibly be regarded as a functional change) as a supplementary means of differentiating the various types.

Addis[13] has advocated the classification of "Bright's diseases" according to the number of red blood cells and casts found in the urine. Thus we see that a description of the anatomical lesions of the non-suppurative, bilateral affections of the kidney does not imply that a classification of Bright's disease is necessarily made thereby. In this presentation *the term nephritis is reserved to designate the pathological changes which occur in the kidneys*, whereas *the name Bright's disease is applied to the various clinical pictures which have been customarily grouped about these renal lesions*. The classification of Bright's disease will not be attempted until the last chapter is reached.

Varieties of Nephritis

The simplest and one of the most inclusive and satisfactory groupings of the main types of renal lesions in Bright's disease, patterned after the precepts of Volhard and Fahr (Fahr[15], page 169), is as follows:

1. Glomerular nephritis (primary involvement of the glomeruli, inflammatory nephritis)

2. Tubular nephritis (primary involvement of the tubules, degenerative nephritis, nephrosis)

3. Arterial nephritis (primary involvement of the arteries and arterioles, vascular nephritis, arteriosclerotic nephritis, nephrosclerosis).

Stress is laid on the word primary as indicating that the process begins in the structure named; if the disease persists, all the elements in the kidney become involved, and the lesion assumes a diffuse distribution, that is, all parts of the renal tissue are implicated. This is why, in the past, many authors have insisted that it was impossible to think of distinct glomerular, tubular or arterial nephritis, but that they should all

be regarded as diffuse nephritis. This is true of the advanced stages, when even the pathologist may be unable to determine the original type of nephritis from which the sclerosis of the kidneys has developed. We have, however, sufficient evidence to be certain that in the early stages of nephritis the initial seat of pathological changes is either glomerular, tubular or arterial, and that each type of lesion is accompanied by certain clinical characteristics.

Friedrich Müller[20], in 1905, made a world famous plea to differentiate inflammatory from degenerative renal lesions in Bright's disease. Nephrosis was the term he proposed for the degenerative affections and nephritis for the inflammatory ones. Both the tubular and the arterial changes in the kidney of Bright's disease are, in reality, degenerative processes. By common consent the name nephrosis has been applied only to the morphological changes in the tubules, whereas those in the arterioles are designated as arteriosclerosis.

Glomerular Nephritis

There are two anatomical forms of nephritis in which the primary lesion occurs in the glomeruli; the diffuse and focal varieties. As the names imply, in the diffuse variety all the glomeruli are diseased, while in the focal variety comparatively few are involved.

Diffuse glomerular nephritis always begins as an acute process, confined entirely to the glomeruli. Its subsequent development may proceed along widely different lines (table 33). It is very necessary to bear them in mind in treating cases of acute diffuse glomerular nephritis. It is now generally believed that toxins produced by hemolytic streptococci are responsible for the diffuse forms of glomerular nephritis. This

matter will be taken up in greater detail when the treatment of the renal lesions is discussed at the end of this chapter.

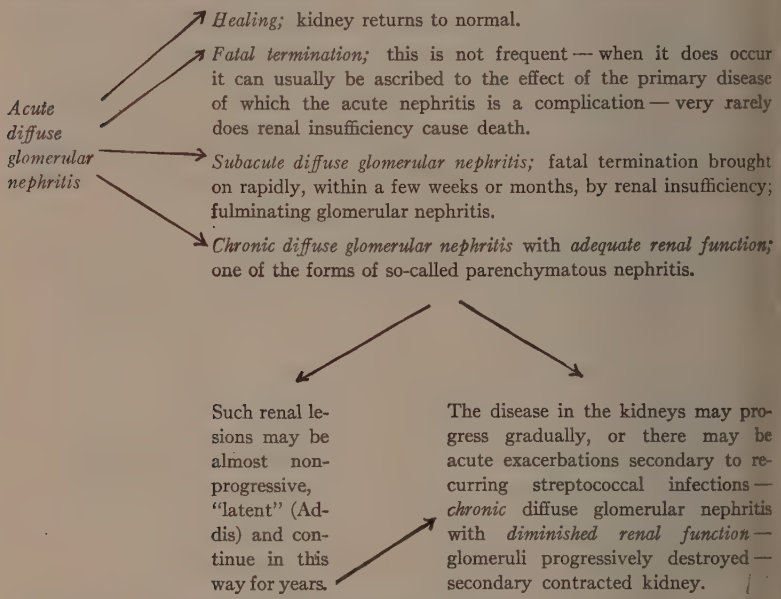
Acute diffuse glomerular nephritis
Healing; kidney returns to normal.
Fatal termination; this is not frequent — when it does occur it can usually be ascribed to the effect of the primary disease of which the acute nephritis is a complication — very rarely does renal insufficiency cause death.
Subacute diffuse glomerular nephritis; fatal termination brought on rapidly, within a few weeks or months, by renal insufficiency; fulminating glomerular nephritis.
Chronic diffuse glomerular nephritis with adequate renal function; one of the forms of so-called parenchymatous nephritis.
Such renal lesions may be almost non-progressive, "latent" (Addis) and continue in this way for years.
The disease in the kidneys may progress gradually, or there may be acute exacerbations secondary to recurring streptococcal infections — chronic diffuse glomerular nephritis with diminished renal function — glomeruli progressively destroyed — secondary contracted kidney.

TABLE 33. — *Diffuse Glomerular Nephritis;* the development of the various morphological types which all originate as acute diffuse glomerular nephritis.

Acute diffuse glomerular nephritis (acute nephritis, acute glomerular nephritis, acute hemorrhagic nephritis, intracapillary glomerulitis). The kidneys often are normal in appearance; they may be slightly swollen and increased in weight; there may be punctate hemorrhages on the surface of the kidney or on its cross-section. By far the more important changes are disclosed on microscopic examination of the glomeruli. These are epitomized by Fahr[15] (page 291) as "diffuse capillaritis of the glomerular tuft". Autopsies in cases of "war-nephritis" afforded Herxheimer[21] and others an opportunity to study the early stages of acute diffuse glomerular nephritis. Of the glomeruli practically all are involved. There is a transient

initial congestion of the glomerular capillaries. The capillary walls become permeable to protein, red and white blood cells. The endothelial cells lining the capillaries proliferate markedly and these, together with accumulating polymorphonuclear leucocytes, fill the lumina of the capillaries, thus crowding out the blood contained in them. The capillary tufts now appear ischæmic, swollen and crowded with nuclei. Although practically all of the glomeruli are affected, they do not necessarily show uniform involvement; the main point is that, while most of them are bloodless, a few of them, or isolated capillary loops in some glomerular tufts, are congested. This accounts for the hematuria, which may persist throughout the course of the disease. If healing takes place, the blood again flows though the capillaries, and the accumulated debris is swept on or breaks through the capillary walls to escape in the tubules. This alternate congestion, anemia and reëstablishment of the circulation is the cause of the bewildering sequence in which hematuria is followed by a diminution in the number of the red blood cells in the urine and this by the return of the hematuria and the final elimination of blood from the urine. The interpretation of these findings may be gathered from the above exposition and has been alluded to previously under hematuria. If the acute diffuse glomerular nephritis does not heal, it goes over into one of the several forms mentioned in table 33 which are described subsequently. The tubules and the interstitial renal tissue are practically free from pathological changes. The morphological lesions are confined to the glomerular capillaries and consequently have been designated as intracapillary glomerulitis to distinguish them from subacute nephritis in which the extracapillary changes of the glomerulus are characteristic. The term "intracapillary" was

first suggested by William H. Welch[22] in 1886. A fatal termination in acute glomerular nephritis is rare; when it occurs it can be ascribed usually to the effect of the primary disease of which the acute nephritis is a complication; death due to renal insufficiency in this condition has been described, but it is of exceedingly rare occurrence. Many efforts have been made to demonstrate that in acute diffuse glomerular nephritis changes take place not only in the renal capillaries, but that there is an involvement of the capillaries throughout the body. These efforts have not been successful, but many of us believe that the day is not far distant when it will be shown that in diffuse glomerular nephritis morphological lesions occur in many organs besides the kidneys.

Subacute diffuse glomerular nephritis (fulminating glomerular nephritis, extracapillary glomerulitis). This form of nephritis has, in my experience, been comparatively infrequent. In American texts usually it is not mentioned at all, and "subacute" serves to describe a nephritis that simply is prolonged beyond an acute stage, while in reality the originators of this term had in mind a form of nephritis lasting longer than an acute nephritis, but terminating fatally within a comparatively brief period. According to Löhlein[23], the first case of subacute nephritis was described by Marchand in 1882; Löhlein[23] published the first satisfactory anatomical description of this disease in 1907. He thought of this form of nephritis as "Stürmischer Typus" which may be interpreted as fulminating diffuse glomerular nephritis. Clinically, the distinguishing feature of these cases is that within five weeks to as many months they succumb to a rapidly advancing renal insufficiency. Most of the glomeruli are bloodless, the glomerular tufts are hyalinized, and between the tuft and Bowman's capsule epithelial crescents

are formed. The latter are derived by active proliferation of the epithelial cells lining Bowman's capsule, which become mixed with fibrin and leucocytes; it is because of the accumulation of these products of inflammation wedged in between the glomerular tuft and Bowman's capsule that the name extracapillary glomerulitis has been applied to this form of nephritis. The glomerular capillaries are destroyed by hyalinization and by compression, and in a comparatively brief period some of them become partially fibrosed. As the glomeruli are affected and their function diminishes, secondary changes necessarily ensue in the tubules; these become lined by a very low layer of epithelium and are considerably dilated. In more advanced cases the tubules may collapse and be lost in the surrounding connective tissue.

Chronic diffuse glomerular nephritis (chronic diffuse nephritis, one of the forms of chronic parenchymatous nephritis, chronic glomerular nephritis, chronic interstitial nephritis, secondary contracted kidney). In this form of nephritis, in contradistinction to the acute type, the tubules and the interstitial tissue are involved as well as the glomeruli. A prolonged interruption of function of any part of the renal element, glomerulus or tubule, entails an atrophy of the remainder of the structure. As indicated in table 33, from the clinical point of view, two main types of chronic diffuse glomerular nephritis may be distinguished; these merge imperceptibly one into the other according to the number of glomeruli that have been destroyed. There is the *compensated stage*, when renal function is adequate, and the *decompensated stage*, when renal function is considerably impaired. It is obvious that it is useless to attempt a sharp distinction of one from the other.

Macroscopically, in the early stages, the kidneys have been

described as the "large white kidney". This term should not be used, since the kidneys in tubular nephritis (nephrosis) and in fulminating nephritis (subacute nephritis) have the same appearance. The kidneys are large, soft, smooth, of a pale yellowish or greyish white color; they may have a diffuse or spotted yellowish or reddish discoloration, depending upon the presence of fatty and lipoid changes and congestion. Later in the course of the disease connective tissue replaces the destroyed renal parenchyma, and the kidney becomes very small, irregularly shrunken, its surface is rough and its capsule adherent. This constitutes the *secondary contracted kidney.*

Microscopically, the glomeruli may show much the same changes that have been described for intracapillary glomerulitis, as well as extracapillary changes; epithelial crescents may be found but are not nearly as widespread as in the fulminating cases. When the glomeruli no longer can recover from the inflammatory process, they become hyalinized, a single capillary loop at a time, until only a homogeneous, hyaline ball remains. This process may go on rapidly or very slowly. The hyaline ball may be surrounded by laminated connective tissue derived from Bowman's capsule. Subsequently the hyalinized glomeruli have a tendency to be absorbed and may disappear largely. The remaining glomeruli undergo a compensatory hypertrophy; they are large and contain many cells; their structure is delicate, and they give the impression of great functional efficiency. The time interval between the early and the terminal stages of this process varies greatly. A contracted kidney, so deplete of functioning glomeruli that death ensues because of renal insufficiency, may develop within as short a time as two years. On the other hand, kidney function may remain adequate and, in spite of albumin, casts and red blood

cells in the urine, such cases may live on for twenty years and more.

The tubules that remain in connection with the surviving glomeruli are dilated and lined by flattened epithelium. It is a question whether such changes are to be regarded in the nature of compensatory hypertrophy corresponding to that of the surviving glomeruli, or whether they are degenerative in character. In addition, some tubules show an excessive growth of their epithelial lining; also, new tubules are formed; thus, adenomatous-like masses may be produced. As was noted for the glomeruli, many tubules disappear to be replaced by interstitial connective tissue.

In chronic diffuse glomerular nephritis of long duration the arteries of the kidney are prone to show signs of arteriosclerosis, and the arterioles are involved, but to a lesser extent. When such changes do occur, often it is very difficult to distinguish these cases from those of primary vascular origin. Baehr and Ritter[24] have demonstrated recently that the number of patent arterioles in secondary contracted kidneys is diminished very markedly. They add that it is not only the diffuse parenchymal disease that is responsible for the shrinkage of the renal tissue, but also that the complicating arteriolarsclerosis plays a very important rôle in the production of the secondary contracted kidney.

Focal glomerular nephritis accompanies infectious diseases. It occurs in two forms:

(1). *Focal infectious glomerular nephritis* — focal hemorrhagic glomerular nephritis (Volhard), focal non-embolic nephritis, infectious nephritis (Munk), hemorrhagic catarrh (Wagner), benign hemorrhagic nephritis (Baehr).

(2). *Focal embolic glomerular nephritis* — embolic nephritis,

embolic hemorrhagic nephritis, embolic non-suppurative focal nephritis (Löhlein), embolic glomerular lesions of subacute bacterial endocarditis (Baehr), multiple glomerular embolization (Fishberg).

Focal infectious glomerular nephritis was first described in this country by O'Hare and Walker[25] and a little later by Baehr[25] the latter using the title of "a benign and curable form of hemorrhagic nephritis". He says that attention was first seriously called to its existence by the German clinicians, Scheidemandel and Volhard. In the course of acute infectious diseases, hematuria, albuminuria and various kinds of casts may occur without any of the manifestations, such as edema, hypertension, diminished renal function or uremia, that are characteristic of the diffuse form of glomerular nephritis. Fahr[15] believes that the cause of the kidney damage is to be found in the effect of the circulating bacteria on the glomerular capillaries, while Munk[26] expresses himself in favor of the view that the kidney lesion is the result of bacterial toxins. It is true that bacteria may be cultured from the urine in this condition, but it is conceded that urinary cultures are positive in the same infectious diseases when the kidneys are free from pathological changes and show no hematuria. Any form of infection may be the source of the bacteria which cause this form of nephritis. Special stress has been laid on tonsillitis and other types of sore throat, but it has been found in typhoid fever, erysipelas, pneumonia, influenza, measles, malaria, tuberculosis, etc. In some of these conditions it may be that the bacteria, which bring about the changes in the kidney, are not those that cause the primary disease, but are secondary invaders. The changes in the glomeruli have been described as focal, inflammatory lesions; on the other hand, it has been

stressed by Munk[26] that no such lesions are to be found. Munk[26] believes that some toxic action renders the capillary wall of the glomerulus pervious to the red blood cells, and hence he subscribes to the idea of Wagner, whom he quotes, that this condition should really be thought of as "hemorrhagic catarrh". In the tubules frequently there is cloudly swelling, some necrosis and desquamation of the epithelial cells. The bacteria may be demonstrated within the tubules. Blood is present within Bowman's capsule and the tubules. One of the outstanding features in this condition is that not all the glomeruli are involved but only a comparatively small number. These lesions usually heal without leaving any traces. The healing takes place when the original focus of infection is eradicated. Volhard[27] has distinguished two stages of focal glomerular nephritis, an acute stage and a chronic stage. Both of these are benign, and the hematuria and albuminuria, characteristic of either one, disappear when the persistent, or recurring, primary, infectious focus is removed successfully. It may be this form of nephritis that has been described by some authors as an epidemic albuminuria. There may be areas of infection in the interstitial tissue as well as in the glomeruli. These consist of lymphocytic infiltration. Occasionally, such lesions predominate and the condition has then been called *acute* or *septic interstitial nephritis*.

Focal Embolic Glomerular Nephritis. — This form of nephritis was originally described by Löhlein[28]. Baehr[29] verified Löhlein's observations and established the fact that bacterial emboli from endocardial vegetations were the cause of these renal lesions. Focal embolic glomerular nephritis occurs almost exclusively as a complication of subacute bacterial endocarditis; it is found regardless of the variety of bacteria affecting the endocardium.

Inspection reveals small hemorrhages, irregularly distributed, as the characteristic change; in long standing cases, scars, resulting from healed infarcts, may be present. On microscopic examination only a minority of the glomeruli are involved usually, though occasionally as many as 90 per cent. may show lesions. As a rule, only a few of the capillaries in any glomerulus are affected and this, coupled with the fact that many glomeruli are not implicated at all, explains the reason why renal function is so well preserved in this disease. The lesions are infarcts due to the lodgement of emboli in the glomerular capillaries. The corresponding part of the glomerulus shows cellular necrosis and subsequently hyalinization. There is very little inflammatory reaction in the surrounding tissues. The injured capillaries frequently rupture, and blood is found in the corresponding Bowman's spaces and in the tubules. If a glomerulus is destroyed completely, the dependent tubules atrophy and disappear, being replaced by fibrous tissue.

Baehr and Lande[30] describe instances of acute diffuse glomerular nephritis occurring as a complication of bacterial endocarditis. It is, therefore, important to know that, while hematuria in the course of this disease usually is significant of focal embolic glomerular lesions in the kidney, there are some instances in which the acute diffuse form of glomerular nephritis is present instead. In 77 autopsies, Baehr and Lande[30] found this to hold true in 9 cases. This acute diffuse glomerular nephritis apparently had progressed to the subacute variety with its typical extracapillary lesions, rapidly advancing renal insufficiency and fatal termination through a retention of urinary excretory products. The advancing change in the renal pathology may be slower, and a secondary contracted kidney occasionally is the ultimate condition.

Tubular Nephritis

In certain forms of Bright's disease the epithelial cells lining the tubules are the primary and principal, though not the exclusive, site of the pathological changes within the kidney. These anatomical lesions are regarded by many pathologists, though not by all, as being degenerative in nature in contrast to the inflammatory processes characteristic of glomerular nephritis. In 1905 Friedrich Müller[20] proposed the term, nephrosis, for degenerative changes in the kidney. Degenerative processes may occur in the epithelial cells of the glomeruli and the tubules and also in the arteries and arterioles. By common consent the name, nephrosis, has come to be applied to the tubular affections, and the vascular pathology has been put in a separate category. Nephrosis literally means "full of kidney substance"; this is not very descriptive, since it might include many forms of Bright's disease as well as other types of kidney pathology. Because the various forms of so-called nephrosis vary very widely in regard to symptoms and signs and have only the location of the pathological changes within the kidney in common, it would seem better to designate this type of lesion as tubular; inasmuch as everyone is not agreed in regard to whether the tubular changes are degenerative or inflammatory, and since the word nephritis is looked upon as meaning the pathology of the kidney occurring in Bright's disease, it would seem advisable, at the present moment, to speak of these conditions as tubular nephritis. The term nephrosis has come to be associated with a certain clinical syndrome and not with tubular lesions of the kidney in general. These are the cases, so widely described under the terms of "lipoid nephrosis", "genuine nephrosis", "chronic nephrosis", etc., for which it is

desired to retain the name nephrosis in this presentation. The wide diversity in the relation between kidney lesion and clinical picture in these cases is apparent in the observations of Christian[31], who found that the signs and the symptoms of such cases may exist in spite of the fact that the kidneys showed no corresponding anatomical lesions.

Volhard[27] (page 335) says: "Histologically the pure degenerative nephropathies, called nephroses, represent a type that may be designated as tubular nephritis in contradistinction to vascular nephritis". This is the stand we wish to assume in regard to the renal pathology. The clinical picture of the various forms of Bright's disease in which the tubular lesions predominate is not a constant one, and we would agree completely with Wolbach and Blackfan[32], when they say: "While offering no substitute, we believe that any name implying a renal origin such as nephrosis or tubular nephritis is not appropriate to this disease". In the analysis of Bright's disease, as offered in this book, the pathology of the kidney is regarded as one of the component elements of the clinical picture, nor is it implied that the renal lesions are the pivotal point about which these maladies are centered.

A better understanding of the matter possibly may be arrived at on the basis of the fact that the tubular forms of nephritis (or nephroses) all have a very similar renal histology but differ greatly in their clinical symptomatology. Such variations may be ascribed to the extra-renal effect of the toxic material that is responsible also for the lesions in the kidneys. Regarded in this light, the *tubular forms of nephritis* may, from the clinician's viewpoint, be classified as follows:

1. *Albuminuric;* nearly all forms of tubular nephritis exhibit albuminuria; there are those in which this is practically the

sole sign of Bright's disease; these often are spoken of as "febrile albuminuria", though this term does not include all the cases that it should.

2. *Edematous;* edema is the predominating feature; these cases constitute the form of tubular nephritis generally thought of by writers on the subject of nephrosis (lipoid nephrosis, chronic nephrosis, genuine nephrosis, diabetes albuminuricus of Epstein); amyloid degenerative changes of the kidney may be included in this category.

3. *Anuric;* characterized by advanced changes (necrosis) in the tubular epithelium; met with almost exclusively in bichloride of mercury poisoning.

4. *Hypertensive and convulsive;* the only well known example is that of the tubular nephritis found in the toxemias of pregnancy.

The above is given to show that there may be various clinical aspects accompanying tubular nephritis and that in describing the pathology of the kidney we do not account for these signs and symptoms. In fact, such a conception puts the cart before the horse, because the constitutional pathology is more likely to characterize this type of Bright's disease than are the anatomical changes in the kidney.

In giving a brief description of the pathology of tubular nephritis the plan of Fahr[15] is followed; he believes that all the tubular lesions are much alike, the differences depending largely upon two factors; first, the intensity of the poison which determines the degree of involvement of the tubular epithelium; and second, the constitutional abnormalities which may account for the material, fatty, lipoid, amyloid or other, with which the renal parenchyma becomes infiltrated.

Tubular nephritis may be divided into three stages, which

may progress from one to the other very slowly or with extreme rapidity according to the characteristic effect of the cause (slow effect of jaundice, rapid advance in bichloride of mercury poisoning); healing and complete restitution to normal may occur at any of the three stages, when the etiological factor is done away with; in some instances there are engrafted, according to Fahr[15], either by infiltration from other sources or through lack of normal metabolic processes within the kidneys themselves, various substances such as lipoid, fatty or amyloid material, hemoglobin, bile, calcium, etc. These substances then characterize the tubular nephritis and have led to such terms as lipoid and amyloid nephrosis.

The three stages which constitute the advancing pathological process of tubular nephritis are:

1. Albuminous or granular degeneration
2. Hyaline degeneration
3. Necrosis.

First Stage: Albuminous Degeneration (granular degeneration, cloudy swelling). — There is granular degeneration of the cells of the tubular epithelium, usually most marked in the convoluted tubules; the cell outlines, their nuclei and the remainder of the kidney substance show no change or only very little. The clinical condition corresponding to this kidney lesion has been generally known as febrile albuminuria; albuminuric tubular nephritis is the term used here.

It is certain that *albuminuric tubular nephritis* accompanies most febrile states, the albuminuria being much more marked in some (e.g., lobar pneumonia, cerebro-spinal meningitis) than it is in others. However, this change in the renal epithelium of the tubules and the albuminuria occur under many other circumstances; jaundice, physical effort, hemoglobinemia and,

at times, with various medications. Albuminuria and hyaline and finely granular casts are the only symptoms referable to the kidneys; the renal lesion heals without difficulty, and it is doubtful whether this type of nephritis is really of sufficient importance to be included as one of the forms of Bright's disease. While the glomeruli are not involved anatomically, they must be affected functionally, as the albuminuria can be accounted for in no other way. In this connection it is interesting to note that Munk[26] describes "veronal nephrosis" as a severe form of tubular injury in which albuminuria is absent.

Second Stage: Hyaline Degeneration. — Hyaline droplets are found in the epithelial cells of the tubules. Certain poisons are believed to induce the progress from the albuminous to the hyaline stage of degeneration, those of diphtheria, tuberculosis, malaria, enteritis, syphilis, streptococcus infections and others. Here, as in the albuminous degeneration, albuminuria and cylindruria are the only clinical symptoms worthy of note.

Third Stage: Necrosis. — The conspicuous lesion is the destruction of the tubular epithelium, usually most marked in the proximal convoluted tubules, though the remaining epithelial cells are involved also; the nuclei of the cells can be found no longer; the desquamated cells obliterate the lumen of the tubules to a greater or less extent.

Many causes are mentioned as responsible for the necrotic form of tubular nephritis, diphtheria, cholera, malaria, dysentery, poisoning by uranium, chromium, veronal, sulphuric acid, hydrochloric acid, salvarsan and others. From the clinical aspect there is only one frequent cause and that is *mercury poisoning* producing *anuric tubular nephritis.*

Anuric Tubular Nephritis. — There are a few very characteristic features in this condition that are worth considering:

A. This is almost the only kidney lesion in which deposits of calcium are found; they occur principally in the convoluted tubules and the ascending limb of Henle's loop; the cause of the calcification is not known. The cells regenerate very rapidly; Hunter[33] was able to show almost complete restoration to normal in a patient who succumbed to extra-renal factors two weeks after mercury poisoning.

B. A very much diminished sodium chloride content of the blood, as low as 114 mg. per 100 c.c., is characteristic of bichloride of mercury poisoning (Lewis and Rivers[34], Killian[35]). Trusler, Fisher and Richardson[36], from their experiments on dogs, believe this to be the result of the loss of chloride because of vomiting. Fishberg[18] does not subscribe to this, "— for one does not usually encounter such low chloride values in uremia due to other causes despite equally severe vomiting".

C. Anuria develops very rapidly in bichloride of mercury poisoning. This has been ascribed to the stoppage of the tubules by the accumulated debris from the epithelial cells. This is not an entirely satisfactory explanation, and the low concentration of chlorides in the blood or a functional disturbance of the glomeruli may be, in part, responsible for the anuria. Richards[37], on the other hand, believes, on the basis of experimental observations, that mercury poisoning is accompanied by glomerular polyuria, and that the lack of passage of urine into the bladder is explained by the drawing back into the blood of the urine through the damaged tubular epithelium without opposition or discrimination.

D. In spite of anuria and a mounting non-protein nitrogen content of the blood and tissues, the blood pressure does not increase appreciably. Janeway[38] records a rise from 130 mm. on the first, to 168 mm. on the fifth day of bichloride poisoning;

Fahr[15] mentions a blood pressure of 160 mm.; these comparatively mild instances of hypertension represent the maximal values exhibited. They do not approach the levels found in acute diffuse glomerular nephritis and many cases of primary and secondary contracted kidneys.

Edematous tubular nephritis is the name given here to the disease which, when mentioned as a clinical entity, has been variously spoken of as chronic nephrosis, lipoid nephrosis, genuine nephrosis, diabetes albuminuricus. It is very difficult to be exact in describing the pathology of this form of Bright's disease, for we do not know the seat of the primary morphological changes; the kidney, the blood proteins, the thyroid and the liver all have been mentioned as possibilities. Perhaps a brief description of the clinical picture of this malady may help to clarify this matter. It may be gathered, especially from Christian's[31] observations, that this is not necessarily a renal disease. Christian[31] noted cases in which the typical renal lesions were present without any of the clinical signs and others that, during life, gave pathognomonic evidence of nephrosis, while at autopsy the kidneys failed to show the expected pathology. Such findings as these make it clear that it is much more logical to look upon nephritis as Bright's disease, until such a time shall arrive when a more exact knowledge of these conditions will enable us to apply a satisfactory nomenclature.

Symptoms and Signs of Edematous Tubular Nephritis. — In considering these, it must be borne in mind that we are not certain whether this symptom complex is primarily a disturbance of the cholesterol or protein metabolism, a primary infection or a disease originating in the kidneys. Opinions on this subject vary so widely as to make it impossible to arrive at a satisfactory conclusion. Consequently the individual

symptoms and signs are presented so that the clinical picture may be recognized.

Age. — The condition is relatively frequent in children. Christian[31] was able to collect only 18 reported cases in adults.

Onset. — This is usually insidious, though Wolbach and Blackfan[32] have observed a sudden beginning of the disease associated with vomiting.

Edema. — This is the outstanding feature of the condition. There is a marked subcutaneous accumulation of fluid which pits readily; ascites is almost constantly present, and there may be fluid in the pleural cavity. Here, as in other forms of nephritis, the ascites invariably precedes the hydrothorax, the reverse being true with passive congestion brought on by cardiac insufficiency.

Albuminuria and Blood Proteins. — These have been discussed in earlier parts of this chapter and will be taken up again in the section on edema. The marked diminution of albumin in the blood and the reversed albumin-globulin ratio are the outstanding features. The albuminuria originates in the glomeruli, which shows that, in spite of the predominating pathology in the tubules, there must be some disturbance in the composition of the blood proteins or in the glomerular capillaries rendering the latter permeable to the albumin and globulin in the blood stream. It is interesting to note, in this connection, that Munk[26] finds that in veronal nephrosis, although the tubules are damaged to a great extent, there may be no albuminuria.

Casts. — These may be present in small or large numbers; there may be all varieties of casts except those containing red blood cells.

Hematuria. — Typically, no red blood cells are found in

the urine; however, there are many exceptions to this rule, and the presence of red blood cells in the urine does not contraindicate the diagnosis of an uncomplicated edematous tubular nephritis or nephrosis. When this occurs, it must be borne in mind that there may be a mixed nephritis, that is, one in which there is a glomerular as well as a tubular involvement.

Doubly Refractile Lipoids. — These may appear in the urine and be present in some of the casts. They are supposed to be derived from the tubular epithelium. However, the curious fact has been established that, even though this substance may be present in the urine during life, there may be no deposit of doubly refractile lipoids found in the kidney at autopsy.

Cholesterol of the blood is increased markedly. This has been discussed in an earlier portion of this chapter.

Kidney function is normal as far as the power of concentration of the urine and the non-protein nitrogen and urea nitrogen of the blood are concerned. However, the ability to dilute the urine is absent, and there is a retention of water and sodium chloride. The specific gravity of the urine usually remains at a high level, in the neighborhood of 1.025.

Blood pressure usually is given emphatically as normal, and this low level of the arterial tension is regarded as typical of a tubular nephritis. There are a considerable number of exceptions to this statement, and the finding of a higher blood pressure need not necessarily prevent confidence in the diagnosis. Thus, Wolbach and Blackfan[32] note blood pressures as high as 175 in children, Volhard[27] notes blood pressures up to 140 and Rosenberg[39] as high as 145. The problem of relation of blood pressure to renal disease should not be regarded too dogmatically with the idea that glomerular lesions are accompanied by arterial tension, while tubular lesions are not. Cer-

tain exceptions are mentioned above, and it is worth bearing in mind that in the tubular renal lesions accompanying the toxemia of pregnancy, the blood pressure may be extremely high, and that in glomerular nephritis, especially in children, there may be no rise above the normal in the arterial tension.

Eye grounds show no variation from the normal.

A low basal metabolic rate is considered by some to be characteristic of edematous tubular nephritis. But, in the first place, it is not constantly found, and, in the second place, according to Aub and Du Bois[40], it may be expected in an individual whose body surface is calculated on a basis of distention by, what is metabolically speaking, an inactive material, that is, the edematous fluid. On the other hand, the thyroid gland often reveals anatomical evidence of functional exhaustion; this may account for the low basal metabolic rate and the success of thyroid medication in some instances.

Clinical Course of Edematous Tubular Nephritis. — The clinical course of edematous tubular nephritis is characterized by recurring attacks of edema and ascites, which lead to a fatal termination within a few years or even a few months.

The cyclical nature of this condition is very evident clinically (Murphy and Warfield[41]); it may be noted also anatomically in the kidneys. Wolbach and Blackfan[32] point out that the effect of the tubular lesions in the kidneys is not cumulative, and that, unless there is complete necrosis of large portions of the tubules, the kidney returns, to a greater or less extent, to a normal condition; subsequently, with exacerbations of the disease, the kidney tissue again goes through the cycle of albuminous, hyaline, fatty and, possibly, necrotic degeneration, so that at autopsy extremely variable pictures may present themselves.

The duration of the disease and its outcome vary a great deal. Christian[31], in commenting on the data of the reports in adult cases, notes that the average duration of the disease was 8.8 months. At the New York Post Graduate Hospital, on the Children's Service, no cases have lived longer than six years. Davison and Salinger[42], on the other hand, report that six of their twenty patients have recovered, and that five of these have been well for more than seven years. Mackay and Johnson[43] report a case of "lipoid nephrosis" in a boy, ending fatally at 19 years of age, the nephrosis having existed for 17 years. In my own experience among adults I have witnessed marked extremes: one patient, after seven years of an edematous tubular nephritis, has been perfectly well, free from albumin and edema, for the past two years, while another patient, a young woman, died within one year after the onset of her disease from what was, clinically, a typical secondary contracted kidney with renal insufficiency. Recoveries apparently occur; they are rare; in general, it may be said that most of the cases die within three years or less.

These patients have a distinctly lowered resistance to infections. A recurring pneumococcus peritonitis is the most common cause of death. Besides peritonitis, empyema and septicemia have been noted frequently. Next to the pneumococcus, the hemolytic streptococcus is the most usual invader.

In diffuse glomerular nephritis the symptoms of nephrosis, or edematous tubular nephritis, may occur. The glomerular nephritis is then spoken of as having a nephrotic component (nephrotischer Einschlag). The reverse also may be true, namely, that an edematous tubular nephritis subsequently may be complicated by a diffuse glomerular nephritis.

Gradually it is being recognized that this form of tubular

nephritis may terminate in a secondary contracted kidney. Clinically, this manifests itself principally by a lowering of the specific gravity of the urine, an increase in the non-protein nitrogenous constituents of the blood, occasionally also by elevation of the blood pressure and, at times, by the other symptoms characteristic of a sclerotic kidney associated with renal insufficiency. Munk[26] claims that he was the first to note this possibility. Kaufmann and Mason[44] have recorded a case of this sort. Clinically, I have observed such a renal sclerosis develop very rapidly (within a year). However, the formation of a sclerotic kidney as the sequence of an edematous tubular nephritis is not an inevitable result, as may be seen from the case of Mackay and Johnson[43], which was free from any clinical evidence of a secondarily contracted kidney after the disease had existed for 17 years.

Some cases, at autopsy, show extensive amyloidosis; this is not to be wondered at, since prolonged suppuration or malignant disease may be complicated by an edematous tubular nephritis, and the two conditions thus may have a similar origin.

Pathology of the Kidney in Edematous Tubular Nephritis. — It should be stressed at the outset of this discussion that the anatomical lesions of the kidneys in this disease are not to be regarded as the primary cause responsible for the signs and symptoms. Genuine nephrosis or edematous tubular nephritis is a clinical conception embracing a considerable number of possible anatomical changes in the blood proteins, the liver, the thyroid gland and elsewhere in addition to those found in the kidney. The clinical symptoms may occur without parallel changes in the kidney and vice versa.

The kidney in edematous tubular nephritis usually is found

to be large, of a whitish or yellowish color, depending upon the amount of fat within it; this constitutes one of the numerous forms of large, white kidney described by the older authors. The capsule strips readily, and, on section, the yellowish color of the cortex, indicating the presence of doubly refractile lipoids, is the outstanding feature. On microscopic examination, as might be expected from the cyclical character of this disease, all of the stages of tubular nephritis may be found; the albuminous degeneration, the hyaline droplet degeneration and necrosis. The characteristic finding is the presence of fine fat globules, doubly refractile in character, in the basal parts of the epithelial cells. The order of the intensity of the involvement is the proximal convoluted tubules, then the distal convoluted tubules, to a lesser extent the arms of Henle's loop, and rarely the collecting tubules.

The glomeruli formerly were regarded as free from disease. Recently there have been some observations pointing to the presence of lesions in the glomeruli. Thus, Bell[45] notes that the glomeruli are never normal, but that there is some increase in the glomerular endothelial cells and some thickening of Bowman's capsule; in some instances, the changes characteristic of diffuse glomerular nephritis are present; in general the capillaries of the glomeruli are not obstructed. In this connection the opinion of Elwyn[46] may be quoted that "lipoid nephrosis always begins as an acute diffuse glomerular nephritis and that the earliest lesions of this condition are to be found in the glomeruli". On the other hand, Shapiro[47] shows that in some cases of "pure lipoid nephrosis" there is no lesion of any kind demonstrable in the glomeruli, and that, consequently, there is no reason to suppose that the tubular changes necessarily must originate in glomerular damage.

Necrosis of tubular cells usually is followed by regeneration. In some instances, where this does not occur, tubular structures are replaced by connective tissue, and corresponding glomeruli may undergo hyaline degeneration and sclerosis. In this way a secondary contracted kidney may develop.

The deposit of lipoid material is not confined to the tubular cells but may be found in the interstitial kidney tissue and also in the liver, suprarenal glands, lymph nodes and spleen (Alter[48], Rachmilewitz[49]). This would indicate that the disturbance in the lipoid metabolism is a constitutional affection and is not confined to the kidneys.

Pathology of the Thyroid Gland in Edematous Tubular Nephritis. — Wolbach and Blackfan[32] mention changes in the thyroid and describe absence of colloid, atrophy of the thyroid tissue, desquamation of the epithelial cells and extreme vascular engorgement. They believe that the same changes are found in other diseases, such as scarlet fever, small pox, diphtheria, measles, etc., and that they are indicative of exhaustion following excessive functional demand in these diseases. They believe that "the thyroid lesion is probably a manifestation of functional exhaustion and therefore probably is neither cause nor direct consequence of the kidney damage".

In regard to the *pathology of the liver*, Wolbach and Blackfan[32] say; "slight atrophy and degeneration of the hepatic cells may also be interpreted as effects of overtaxed functional activity consequent to the loss of blood proteins".

Arterial Nephritis

Synonyms. — Primary involvement of the arteries and arterioles, vascular nephritis, arteriosclerotic nephritis, nephrosclerosis, primary contracted kidney.

In the section on chronic diffuse glomerular nephritis we saw that, following the gradual destruction of the renal parenchyma, the arteries and arterioles always become involved and that their obliteration contributes largely to the destruction of the renal tissue that leads to the condition known as secondary contracted kidney. There is one form of primary disease of the arteries and arterioles of the kidney, that greatly resembles the lesions as found in the secondary contracted kidney, so that, at times, the pathologist in the later stages of these conditions cannot be sure whether the original site of the renal involvement has been in the vascular or parenchymal tissue of the kidney.

This type of vascular degeneration is an arterio-, or arteriolo-sclerosis; it is also spoken of as the benign form of vascular nephritis. It has been shown in recent years that sclerosis of the arterial elements in the kidney is not the only type of vascular involvement that this organ is subject to, but that there may also be necrosis and inflammation. The latter changes have been designated as malignant sclerosis by some authors and as arteriolar necrosis by others; the latter is the term used in this book. The whole subject of vascular nephritis, as it has developed from the time of Gull and Sutton in 1872, is extremely intricate and teeming with important problems in relation to arteriosclerosis that await solution.

There are two types of vascular nephritis; the first of these is the arterio-, or arteriolo-sclerosis of the renal vessels, the second consists of a necrosis of the arterial wall associated at times with an inflammatory reaction, an arteritis and periarteritis. These constitute the so-called benign and malignant forms of nephrosclerosis as described by Fahr and others.

Sclerosis of the Arteries and Arterioles, Benign Nephro-

sclerosis. — This theoretically is made up of two affections. The one is an involvement of the arterioles, an arteriolosclerosis, the other a disease of the larger vessels, called the arteries in order to differentiate them from the arterioles. The importance of this differentiation dates from the observations of Sir Clifford Allbutt, who distinguished between senile, or decrescent arteriosclerosis, which usually involves the larger arteries, and an arteriolosclerosis, which is the involvement of the smallest arteries immediately preceding the capillaries, that is, the arterioles. The former comes on as part of the normal process of growing old and may develop also prematurely, so that an individual of 30 or 40 years may have the senile arterial changes of a person of 70 or 80. The arteriolar lesions, on the other hand, usually are the sequel of an increased blood pressure. Continued hypertension invariably produces pathological changes in the arteries, and while the entire arterial tree may be affected, the lesions usually are most marked in the smallest arteries and the arterioles.

Although in some cases of nephrosclerosis the larger arteries are involved predominantly and in others the lesions are confined almost entirely to arterioles, principally the vasa afferentia of the glomeruli, yet a differentiation is not feasible from the practical viewpoint and, consequently, somewhat forced. I agree completely with Fahr that in describing benign nephrosclerosis the two types of disease, the arterial and the arteriolar, should be considered as one.

Gross examination reveals kidneys which in the advanced state have an irregular surface and a markedly adherent capsule. The projections upon the surface are due to the hypertrophy of the functioning kidney parenchyma, the depressions to the puckering incident to connective tissue formation which

replaces the destroyed renal elements. That at the beginning of the process the surface of the kidney is smooth and only later becomes irregular, is self-evident. As the kidneys are permeated with connective tissue and become irregular, they diminish in size and weight, though such primary contracted kidneys usually are not as small as the advanced secondary form of contracted kidney. The color of these kidneys is often red or reddish, and this is probably due to the passive congestion resulting from the myocardial insufficiency attendant upon the high blood pressure which is present so commonly. In the absence of cardiac failure the predominance of hyperplasia of the kidney substance, or of fatty degeneration, may result in a white color in the primary contracted kidney.

In the arterioles the first change noted is a hyaline deposit beneath the endothelium. This usually begins in a patchy way at the junction of the vas afferens with the glomerular tuft The hyaline material spreads and increases, thus greatly narrowing and finally obliterating the lumen of the vessel. In the slightly larger arteries the process begins as a hyperplasia of the internal elastic membrane. This subsequently shows fatty and hyaline degeneration, which, in turn, is followed by connective tissue cell formation, the whole resulting in an extensive thickening of the intima. By this process the lumen of the vessel gradually is narrowed and may be obliterated. Accompanying these changes in the intima, the muscular layer of the media undergoes fatty and hyaline degeneration, and ultimately there is complete disappearance of the muscular elements and replacement by fibrous tissue.

The picture presented by the renal elements themselves is extremely variable, depending as it does upon both the number of arteries and arterioles involved and upon the degree in which

their lumen is narrowed or completely obliterated. The consequence is that certain areas may be totally atrophied, while others have undergone compensatory hypertrophy. As the blood supply in the afferent glomerular arterioles is shut off, the glomerular capillaries become hyalinized and finally appear as a hyaline ball containing the remnants of a few scattered nuclei; in many instances the cells of Bowman's capsule proliferate, and the glomerulus becomes compressed by a concentric layer of connective tissue cells; ultimately the glomerulus is completely fibrosed and disappears in the surrounding connective tissue. The remaining Malpighian bodies may be of normal appearance or become enormously hypertrophied in their effort to compensate for the destroyed glomeruli. The tubules leading from the fibrosed glomeruli undergo a similar change and fuse with the surrounding tissue elements; this is in accord with the well known fact that the tubule does not remain intact when its glomerulus is destroyed, and vice versa. The tubules related to functioning glomeruli may become hypertrophied and thus adapt themselves to the demand for increased activity; their lumen is considerably widened, and they are lined by low, flat, epithelial cells.

All of these findings greatly resemble those of the secondary contracted kidney. The predominance of the changes in the arteries and arterioles in the primary contracted kidney is the main point of differentiation and indicates that here the arteries are the site of the primary pathological lesions, while in the secondary contracted kidney the process begins in the glomerular capillaries.

Arteriolar Necrosis, Malignant Sclerosis. — A great deal of confusion prevails in regard to this form of arterial nephritis because the term malignant has been used to designate a

number of hypertensive and nephritic conditions that cannot be included under one head. Some of these facts have been discussed already on previous pages. Volhard and Fahr[16] in 1914 coined the term malignant hypertension for those cases in which a high blood pressure was complicated by a renal insufficiency; when there was no impairment of renal function, the hypertension was considered benign. This nomenclature was abandoned until it was revived, in a modified form, by Keith, Wagener and Kernohan[50], and more recently by Murphy and Grill[51]. By these authors the fact is stressed that in certain cases of hypertension there is a progressively downward course and a rapid termination, which is not associated necessarily with uremia or even a marked diminution in kidney function. It has been previously pointed out in this volume that the term "progressive" or "severe" in this connection is preferable to "malignant", and that most of the severe cases exhibit a diastolic pressure of 130 mm. of mercury or higher. Murphy and Grill[51] concluded that the so-called malignant hypertension is distinguished from the benign form only in the greater severity of its clinical symptoms and the more extensive arterial and arteriolar lesions. The point is that neither clinically nor pathologically is the dividing line between these types of hypertensive disease sharp enough to warrant the contrast implied in the designations "benign" and "malignant". Furthermore, the situation has been complicated by Fahr, who speaks of certain vascular lesions in the kidney as malignant sclerosis. However, it is generally believed and has been especially stressed by Klemperer and Otani[52], that the lesions in the kidney constituting the malignant sclerosis of Fahr occur in cases of marked, prolonged elevation of blood pressure, especially of the diastolic pressure. Thus, it may be readily

appreciated that the term malignant, as applied to hypertensive states and the various types of vascular nephritis, has assumed an unduly inclusive significance and has been robbed of any distinctive meaning in this connection. A more descriptive term for this particular form of vascular nephritis would be arteriolar necrosis or necrotic arteriolar nephrosclerosis; this indicates the characteristic pathological lesion which differentiaates this condition from the usual form of sclerosis of the arteries and arterioles (benign nephrosclerosis) described in the previous section.

Both the gross and the microscopic examinations of the kidneys reveal two distinct types of lesion in this disease. The first is that described under the heading of arteriosclerosis and is the inevitable sequel to prolonged hypertension; here the changes, notably the granulation and shrinking of the kidney and the obliterating endarteritis, are less pronounced than in the advanced primary contracted kidney because these patients succumb to other kidney lesions before such renal pathology has time to become fully developed. *The second and characteristic change, which stamps this as an individual form of nephritis, is the necrosis and hemorrhagic infiltration of the walls of the renal arterioles and especially of the afferent glomerular arteries.*

Gross examination shows, besides the granular surface and moderate diminution in size, the results of the arteriosclerosis, also petechial hemorrhages, often very profuse, on the surface and on section. Microscopically, we find the arteriosclerotic changes described in the preceding section under the heading of sclerosis of the arteries and arterioles and, in addition, the pathognomonic necrosis of the arterioles, especially of the afferent glomerular arteries. Secondary to the latter lesions, the glomeruli have become affected; there is necrosis of the capil-

lary loops, accumulation of polymorphonuclear leucocytes and a few red blood cells in the Malpighian capillaries and in Bowman's space, and occasionally such cells, mingled with the products of endothelial and epithelial proliferation, are compressed to bring about the extra-capillary formation of crescents, much like those found in subacute nephritis. The problem of why and how these lesions are produced is still a matter of discussion. Some light on this matter is furnished by a study of the clinical course of these cases.

Age. — On the autopsy table arteriolar necrosis is found in younger subjects than is the uncomplicated, so-called, benign arteriosclerosis. Fahr[15] has collected the statistics on this point, and there is thorough agreement on the part of all observers in regard to it. In the series of Klemperer and Otani[52] 72 per cent. of these cases were less than 50 years old, which is the exact reverse of the age incidence of the benign or usual type of arteriosclerotic lesion in the kidney. Fahr[15] believes that the predominance of this condition in younger people points to a toxic agent as a cause of this disease. It would seem to me that, if high blood pressure, especially high diastolic pressure, is regarded as the etiological factor, we should expect the necrotizing arteriolosclerosis to be found in individuals below middle age, since it is among them that the excessively high diastolic blood pressures occur, while in older people the diastolic pressure is prone to be low even when the systolic tension is elevated. Another reason for early death from necrotizing arteriolosclerosis is the fact that renal insufficiency and uremia apparently cut life short within a few weeks of the onset of this disease, while the subject of arteriosclerosis of the kidney lives for many years, and the process advances so slowly that death usually is due to an extra-renal cause.

Clinical Course and Symptoms. — Klemperer and Otani[52] have furnished the most accurate data portraying the clinical picture in cases of arteriolar necrosis of the kidney as verified by autopsy; the facts detailed here are largely from their observations. The essential clinical feature was a preceding hypertension of long duration with elevation of the diastolic as well as the systolic pressure; the average blood pressure in their cases was 212/132. There was a rapid onset of marked renal insufficiency which resulted in death through retention uremia within a brief period. The usual signs of maximal impairment of renal function (especially stressed was the concentration of blood urea nitrogen at a level of 100 mg. per 100 c.c. or higher) and the usual symptoms of retention uremia, vomiting, restlessness, muscular twitchings, somnolence progressing to coma and death, were present. The disease terminated fatally in from five days to five months after the onset. The significance of these signs and symptoms, as far as the pathological process is concerned, is that the changes in the kidneys are of sudden onset and inevitably progressive when they have once begun.

Cause. — Fahr[15] believes that "malignant sclerosis" is brought about by certain poisons that have a specific effect upon the renal arterioles. In this connection he lays stress on lead, gout, tobacco, rheumatism, syphilis and bacterial toxins. Fahr interprets the glomerular lesions as inflammatory and believes, therefore, that there must be a toxic cause for necrosis in the arterioles; he also cites the comparatively youthful age of these subjects in support of this idea. That this is not the inevitable interpretation has been pointed out already in the paragraph on age in this section. The majority of authors, including Herxheimer[53], Löhlein[54], Kaufmann[55], Bell and Clawson[56], Klemperer and Otani[52] and others, think that arteriolar

necrosis is an acute complication of the usual arteriosclerotic process. Klemperer and Otani[52] give a very clear and convincing exposition of this side of the question. The changes, which Fahr describes as inflammatory, they have noted as occurring in severe renal arteriosclerosis, that is, in the advanced stage associated with marked impairment of renal function, and consequently they believe that such pathological lesions may be ascribed to a shutting off of the blood supply from the glomerular capillaries; in other words, that the pathology may be considered to be the result of a pronounced ischemia. Their contention is vastly strengthened by the fact that similar pathological processes are found in the anemic areas resulting on the peripheral side of bland kidney infarcts. The form of nephritis known as arteriolar necrosis, malignant sclerosis of Fahr, may, therefore, be regarded as the result of an acute narrowing of many of the smaller arteries of the kidney which, through a sudden and complete deprivation of the blood supply, entails destructive lesions in the arterioles and glomeruli. This condition is an exacerbation of the usual arteriosclerotic process and occurs in response to a sustained elevation of the diastolic as well as the systolic blood pressure. If Fahr is correct in his contention that certain toxic substances are responsible for the renal pathology in this form of nephritis, it should be an easy matter to reproduce these lesions in animals; however, such experiments have, thus far, not been successful.

Retinitis and Amaurosis of Bright's Disease

The retinal changes accompanying various forms of Bright's disease were termed albuminuric retinitis by Liebreich in 1859, and this name is in use today. In addition to these eye lesions, there is, at times, a rapid loss of vision, usually

transitory, called nephritic, albuminuric, or uremic amaurosis.

Albuminuric retinitis was, until recently, considered a complication of Bright's disease. During the last few years numerous observers have come to believe that separate varieties of retinitis, notably albuminuric, hypertensive and diabetic forms, cannot be differentiated accurately from each other on the basis of the signs in the retina alone. This is the conclusion I have arrived at after a study of a number of such cases.

Martin Cohen[58] believes that the pathological basis for all changes in the fundus rests entirely upon vascular lesions. Fishberg[18], in his monograph, expresses the view that every instance of retinitis is a sequel of hypertension; in proof of this contention he mentions the fact that the types of kidney disease which have no elevation of blood pressure, such as tubular nephritis, focal glomerular nephritis and amyloid disease, are not subject to retinitis. On the other hand, there are two points worthy of note in this connection: Albert Brown[59] was able to demonstrate the presence of retinal changes, including hemorrhages, areas of degeneration and papillitis, in cases of acute febrile toxemia; Leber[60], and others as well, make note of the occurrence of typical albuminuric retinitis in patients who have none of the renal manifestations of Bright's disease. It is probable, therefore, that any disturbance that affects the blood vessels, whether it be hypertension, infectious disease, or the toxemia of Bright's disease, may bring about a so-called albuminuric retinitis.

Albuminuric retinitis presents changes about the papilla, lesions due to vascular involvement and degenerative areas in the retina. These have been described in chapter IX, the part on Hypertension, and are summarized here.

Vascular Pathology. — The arteries become uneven in caliber.

irregular in outline and tortuous; as their walls are thickened, and their lumen encroached upon, or even obliterated, their central light streak is rendered more and more prominent until they assume the so-called silver-wire appearance. Retinal hemorrhages come on slowly or develop rapidly; these may be few or many, small as pinpoints or very large; the shapes of these extravasations of blood vary greatly; they may be round with sharply outlined margins, oblong streaks paralleling the arteries, flame shaped, or may have a distinctly stellate grouping. The hemorrhages secondary to thrombosis of the central retinal artery have to be kept in mind as a possible phase of the condition. The veins become tortuous and show alternate dilatation and contraction; where they are crossed by the thickened arteries, the veins are indented, compressed and may even be obliterated.

Areas of degeneration make their appearance in the retina; these are supposed to be composed of cholesterol deposits; they may be comparatively small in size, of white or yellowish color; when interspersed with blackish pigment they give rise to the name of "moth eaten retina". The vascular changes described in the previous paragraph and the sharply circumscribed oval or round degenerative spots in the retina, when occurring without other retinal lesions, are particularly characteristic of hypertensive states, though not pathognomonic of them. The degenerative spots may become larger, have a feathery outline and are then known as cotton-wool exudates. Frequently the degenerative areas are grouped in stellate formation about the macula.

The *papilla* manifests its first changes in the dimness and progressive obliteration of the outlines of the disk. The papilla and surrounding retina become edematous, and this condition

may be so pronounced that it duplicates the appearance of the "choked disk" so often regarded as almost pathognomonic of brain tumor. Subsequently the edema may disappear, and a white, atrophied, nerve head remain as the only sign of the active process that has preceded it.

Prognosis and Clinical Course. — These depend more upon the disease to which the retinitis is secondary than upon the changes in the fundus oculi itself. There is a tradition that marked albuminuric retinitis means a fatal issue for the patient within two years. There is basis of truth in this statement, but many exceptions occur. In some instances the retinitis clears up completely. Marked retinitis may be associated with a considerable diminution of vision, though complete blindness is rare. Bright, in his original essays, noted the inability of some of these patients to see well.

Martin Cohen[58], on the basis of his microscopical examinations, believes that there is an underlying vascular pathology in all forms of retinitis and consequently suggests that the term *chorio-retinal arteriosclerosis* is far more in accord with the facts than "albuminuric retinitis".

Amaurosis comes on rapidly in Bright's disease, most often as a complication of acute diffuse glomerular nephritis; however, it may occur in any form of hypertensive disease with or without kidney involvement. Examination of the fundus oculi reveals no abnormalities, and the light reflex of the pupils is maintained. Therefore, the pathological change responsible for the blindness is not in the retina or the optic nerve but must be in the brain. Oppenheimer and Fishberg[57] believe that this symptom, and many others characteristic of acute uremia, are brought on by a temporary contraction of the cerebral arteries and arterioles; in this way they account for the fact that rapid

variations of blood pressure and various manifestations of disturbed cerebral function often accompany each other. Many authors subscribe to the idea that edema of the brain may be the underlying pathology; we should not lose sight of the fact that many of these cases are the victims of bacterial infections, the toxins of which may cause injury to the brain as well as to the kidneys. The nephritic amaurosis usually disappears within a day or two, and, subsequently, vision is normal.

Treatment of Nephritis

Since we limit the term nephritis in this volume to the pathological changes which occur in the kidney and do not include the constitutional signs and symptoms, which may manifest themselves in connection with the renal lesions, we shall take up here only the therapeutic measures which affect the pathology of the kidney and no others. The latter will be discussed in the appropriate sections on renal function, edema, uremia, etc.

Treatment of Acute Diffuse Glomerular Nephritis

The control of the lesions in this disease naturally depends on the eradication of the cause, which by its persistence may keep the process in the kidney active and progressive. *The etiology of acute diffuse glomerular nephritis* has not been taken up before this point, because it is so closely related to the treatment of the lesions in the kidney that it seems most logical to discuss the two together. Löhlein, in his early years of activity, was the first to suggest that the *diseases, which were either produced by the streptococcus, or associated with streptococci as secondary invaders, were those that were complicated by an acute glomerular nephritis.* From this, the belief has been developed

gradually that the diffuse form of glomerular nephritis is the result of infection by the hemolytic streptococcus. The bacteria themselves are not found in the urine or the kidneys, and the renal changes are the result of the action of the toxins derived through bacterial activity. Longcope[61], from clinical and experimental data, concludes that some reaction of the kidney tissue, probably allergic in character, is the determining factor in the development of acute diffuse glomerular nephritis. Some authors are convinced that other bacteria besides the streptococcus may be concerned. Thus Fahr[15] is certain that the pneumococcus is responsible for some cases. Scarlet fever, tonsillitis, so-called influenza, erysipelas, diphtheria, tuberculosis and innumerable other conditions, some caused directly by hemolytic streptococci, some only associated with hemolytic streptococci as secondary invaders, have been found to be complicated frequently by acute diffuse glomerular nephritis. From this it is surmised that the hemolytic streptococcus is the organism whose growth within the body is responsible for the toxins which result in the renal changes of acute diffuse glomerular nephritis. Many cases of acute nephritis or acute exacerbations of chronic nephritis were, at one time, supposed to be the result of acute alcoholism or exposure to cold; it is now believed that these factors have a pathological bearing only in so far as they may, through lowered resistance, favor the development of the hemolytic streptococcus at some point within the body. All these facts are important because, in the treatment of the renal lesions of acute diffuse glomerular nephritis, the one and, apparently, only hope for a complete cure lies in healing the primary streptococcus infection and eradicating these bacteria from the body.

Longcope[61] has achieved very satisfactory results, both in

treating the acute processes and preventing exacerbations, in those cases in which the source of hemolytic streptococci was removed successfully by operation upon the sinuses, tonsils and other foci harboring these bacteria. He also notes that the majority of the progressive cases "have had continuous and obvious infections of the paranasal sinuses or nasopharynx, from which cultures have shown persistently, or at irregular intervals, great numbers of hemolytic streptococci".

In our experience, operations performed on the tonsils, the paranasal sinuses and other foci of infection have not resulted in permanently harmful symptoms to the patient with acute or chronic Bright's disease. There may be a transient increase of edema, albuminuria, hematuria and possibly some of the other signs and symptoms, but this disappears within a day or two. Longcope[61] has seen cases where such reactions or exacerbations lasted much longer, but, here too there was an ultimate return, after a prolonged reaction, to at least the preoperative condition. Even though such a temporary aggravation of the symptoms of glomerular nephritis is not to be taken lightly, it seems most probable that an operation of this sort will help to prevent exacerbations and progress of the renal lesions in the following years.

It should be borne in mind that acute diffuse glomerular nephritis is, as a rule, a distinctly self-limited lesion in certain respects. A patient does not succumb to the kidney disease nor to the effects which it produces; there may be acute uremia, marked hematuria or oliguria, but these rarely, if ever, persist to bring about a fatal termination. However, the disease may progress from the acute to the subacute type, at which stage death may occur from renal insufficiency within a period of weeks or a few months, or it may go on to be-

come chronic, giving rise to a chronic diffuse glomerular nephritis.

It is doubtful whether operative procedures should be undertaken during the early stages of acute diffuse glomerular nephritis. They should rather be kept in reserve to be used if the disease becomes subacute or chronic and shows no tendency to heal on its own account. At what point in the course of a diffuse glomerular nephritis operative procedures should be carried out is one that requires fine judgment; the original infection, the nephritis and other complications must be considered in making such a decision.

The most important point in the treatment of acute diffuse glomerular nephritis is the control of the original disease to which the kidney lesions are secondary. Appropriate and energetic measures must be taken to combat scarlet fever, tonsillitis, influenza, diphtheria, etc. Certain other phases of the situation, that may influence the changes in the kidneys, must be considered also. These are diet, rest, drugs, physical therapy, renal decapsulation and prophylactic measures. At the risk of repetition, attention is again called to the fact that only the treatment of the kidney lesions, not that of the extra-renal factors, such as edema, uremia, etc., is being considered at this point.

The dietetic treatment of acute diffuse glomerular nephritis always has consisted of food restrictions aimed at saving the kidney from all possible irritation by substances which must necessarily be eliminated through renal channels. On this account the protein foods, especially meats and eggs, have been withheld. Curiously enough, up to only a few years ago, both milk and bread were allowed in any quantities, but since now it is recognized generally that these foods contain a considerable

amount of protein, they should not be permitted in unlimited amounts in a protein-limited diet. Fats and carbohydrates may be given in moderate amounts, because they are oxidized and eliminated as water and carbon dioxide and are not ultimately responsible for metabolic products that must be excreted by way of the kidneys; besides shielding the kidneys in this way, the carbohydrates and fats prevent the elimination of protein end-products through renal channels by providing calories which the body utilizes readily; thus by functioning as protein sparers they serve to relieve the kidney of much excretory work. For the same reason that the proteins are restricted and the carbohydrates and fats allowed in considerable amounts, i.e., mainly to prevent irritation of the kidneys, the salt intake usually is held down to the minimum; in addition, a restriction of sodium chloride is indicated because retention of salt is associated with the formation of edema, a certain amount of which usually, but by no means always, exists in this form of Bright's disease. Because of the presence of, or tendency to, edema, the fluid intake must be limited also to one or two pints a day.

Volhard[27] and also Lichtwitz[62] have carried this idea of "Schonungstherapie" for the kidney to an extreme. They limit the diet to a pint of fluid and a little fruit daily. The effect of this is to bring irritation of the kidney to a minimum and not only to prevent edema but to cure it, to lower blood pressure and, through these results, to put less strain upon the heart. That the heart possibly deserves more consideration than has been thought necessary hitherto, is shown by the observations of I. Jesse Levy[63], who found considerable cardiac disturbance in cases of acute diffuse glomerular nephritis. Fishberg[18] endorses these dietetic measures and believes he has

achieved good results with them. Briefly, a schedule somewhat as follows may be advised, but should not be adhered to slavishly, and discretion must be used in regard to amounts of food and fluid:

For three days, daily, a pint of bland fluid, with sugar or lactose added, such as lemonade, orangeade, or weak tea and three portions of some easily digested fruit (oranges, grapefruit, prunes, baked apples, etc.) are prescribed. During the next three days the fluid may be increased to a pint and a half, and some starchy foods, such as arrowroot crackers, cornstarch puddings, preserves, sugar, honey and baked potato may be allowed. Subsequently, the food and fluid are increased gradually so that after about two weeks from the onset of the nephritic condition a full diet, moderated to contain about 50 to 70 grams of protein and approximately 1800 calories (for an adult), without the use of spices or salt, may be taken. Later a normal diet may be resumed, but due attention must be paid to the restriction of proteins, if there is persistent albuminuria or renal insufficiency, to the restriction of salt and water in case there is edema, and furthermore, if possible, to the problem of giving sufficient proteins to cover the body's requirements and also the loss of albumin in the urine.

These limitations of the diet meet all therapeutic requirements. It should be pointed out that there is no proof to date that the ingestion of protein, salt, water or other materials is harmful to the kidney in acute diffuse glomerular nephritis. These ideas rest on assumption only. It is a well-known fact that it requires only a few days for the critical phase of an acute diffuse glomerular nephritis to disappear, and that apparently this vanishes regardless of the treatment employed. In view of the brevity of the very acute phase of this disease,

it may be wise to make full concession to the idea that certain foods will irritate the kidney because, for the short time involved, starvation or semi-starvation will do no damage and may be of some benefit.

A more liberal and, I believe, equally effective mode of dietetic treatment is to allow starchy and fatty foods in any quantity. This would include all fruits, whether fresh or cooked, sugar, candy, syrups, jams, jellies, honey, variously flavored cornstarch and tapioca puddings, arrowroot biscuits, butter and all vegetables excluding rice, corn, green peas and baked or lima beans. If we desire to be consistent in excluding protein foods, it should be remembered that bread, rice, cereals and milk, which are advocated so commonly as non-irritating foods for acute renal conditions, are distinctly not in order. The fluid should be given up to at least a quart a day for an adult and need not necessarily be restricted at all unless the edema becomes exceedingly irksome. It should be remembered that water is the blandest and probably the most efficient of all diuretics and that its presence in excess will probably do much to restore the oliguric kidney towards normal function. The fluids may embrace weak tea, weak coffee, decaffeinized coffee, orangeade, lemonade, grape juice and water. It is well to allow a small amount of cream (about a quarter of a pint a day) for flavoring. Mineral waters, so widely advertised as beneficial, are of no particular value and, in fact, are contraindicated, if we wish to eliminate salts from the dietary as much as possible. Following this period of about a week of such food restrictions, when the acute symptoms of hematuria, edema and hypertension are on the wane, a gradual return to a normal diet is indicated.

In some cases, where there was a persistent oliguria or

anuria, Volhard[27] has advocated giving from the fifth day on in the course of an acute diffuse glomerular nephritis one and a half to two litres of weak tea in the course of $\frac{1}{2}$ to $\frac{3}{4}$ of an hour. This is done to spur the inactive kidney on to secrete urine. This procedure, if necessary, is repeated daily for several days; in the interval between the giving of these rather large amounts of fluid, the dry diet advocated by Volhard, as detailed previously, is continued. Volhard has given this method the name of "Wasserstoss", which may be translated as "water punch", a pugilistic term in relation to the kidney. This method of treatment has not met with universal approval and has been thought by some to be productive of harmful results. It is probable that in certain cases it is followed by a diuresis, but it is extremely doubtful whether this would not occur in the normal course of events without such drastic measures.

Rest in bed should, if possible, be continued for at least a month after the albuminuria has disappeared. However, where the albuminuria has not diminished after two months in bed, the patient may be allowed to get up during the third month and gradually resume his occupation, provided this causes no material increase of the albuminuria. Rest is probably one of the most important phases of the treatment, because it makes it possible for the physician to combat the primary focus of infection and to observe the patient for diagnosis as to the possible seat of the streptococcus multiplication.

Medications have very little value in this disease. In fact their use is contraindicated rather than otherwise. The resort to diuretics, especially the mercury diuretics, often is productive of great harm, and it is doubtful whether they are ever beneficial. It must be remembered that the kidney function in acute diffuse glomerular nephritis usually returns to normal

without interference, and that medication, especially the use of diuretics, may be productive of oliguria rather than polyuria (Christian[64]). A full discussion of the use of diuretics will be found in the chapter on edema. Cathartics are the only form of medication that may be of more or less routine value. Mild laxatives containing aloes, phenolphthalein, cascara or mineral oil often are sufficient. More vigorous elimination may be obtained by the salines and may be particularly indicated when edema is a complicating factor. In using cathartics, those containing calomel, or other forms of mercury, should be avoided because of the irritation mercury tends to produce in the kidney tubules.

Physical therapeutics have not proved very successful. The various sweating procedures, rectal irrigations and other measures are not used in a routine way as they were some years ago. It is now recognized that they make the patient uncomfortable, drain his vitality and have little or no beneficial effect upon the kidney itself. The idea that such measures provide compensatory elimination to supplement diminished kidney function has not proved to be valid. Here again it should be kept in mind that the kidneys in acute diffuse glomerular nephritis resume their activities spontaneously, and that either artificial stimulation to promote diuresis, or vicarious efforts at supplementary elimination, are not only unnecessary but may at times even depress kidney function rather than increase it.

Decapsulation of the kidney has been advocated in various quarters, first by Harrison[65] in 1896 and subsequently by Edebohls[66] of New York City, and has been employed sporadically since then. The results have been exceedingly doubtful, and it is our opinion that it is most advisable never to resort to decapsulation of the kidneys as a means of relieving nephritis.

Prophylactic treatment of acute diffuse glomerular nephritis.— This may be considered under two headings; (1) the prevention of acute diffuse glomerular nephritis in those diseases in which a kidney complication is likely to occur, (2) the prevention of recurrence of nephritis in healed cases and the prevention of exacerbations of nephritis in cases where the disease has assumed a chronic aspect.

The prevention of acute diffuse glomerular nephritis in those diseases in which the kidney condition is a frequent complication has received much study but has not, thus far, led to very satisfactory results. It has been mentioned previously that such diseases as scarlet fever, diphtheria, influenza, etc., should be treated with all possible care to make the control of the primary infection as rapid and as thorough as possible. This probably will accomplish more toward the prevention of an acute diffuse glomerular nephritis than any other measure. In the course of these diseases, various diets have been considered of possible value in preventing the occurrence of acute nephritis. The experiments of Popspischill and Weiss[67] on this subject stand out as the most significant. They divided their cases of scarlet fever into two groups; one received a diet of milk, wheat products, fruit, eggs and vegetables, and the other was fed considerable quantities of meat and meat soups. There were 1,186 cases in each group; the children on a vegetarian diet were pale, poorly nourished and depressed, while those on a meat ration were rosy-cheeked, well nourished and full of energy. The number of cases of nephritis, the severity of the nephritis and the character of the nephritis were exactly the same in the two groups; in the milk-fed children there were 116 cases of nephritis, that is 9.78 per cent., and in the meat-fed there were 118 cases of nephritis, that is 9.95 per cent. From

these researches, it is apparent that a prophylactic diet, in the sense of abstinence from meat, reduces the vitality of the individual but does not prevent the occurrence of acute diffuse glomerular nephritis.

Prophylactic treatment designed to prevent the return of nephritis and the occurrence of exacerbations should be carried out in two directions; in the first place, the eradication of all foci harboring hemolytic streptococci, as discussed above; in the second place, the regulation of hygiene to prevent any tendency towards "catching cold" and to avoid a depressed vitality that will favor the lighting up of dormant foci of infection. On this account, the residence in warm, dry climates, especially during the winter months, has been advocated. Southern California and Arizona, and to a lesser extent Florida and the West Indies, are recommended in the United States; in Europe, Egypt has been the favorite resort for these patients. It is doubtful whether a warm climate protects an individual more effectively from acute exacerbations of a nephritis than does careful shielding from infections in colder regions; there may be some sinus infections and other occasional lesions that are much benefited by a dry climate; however, this point will have to be judged by the rhino-laryngologist and need not depend on the verdict of the general practitioner or internist. In my own experience, I have found that proper protection and precautions in the habitual surroundings of the patient are very much more valuable, and an explanation of this may be found readily in the simple fact that human beings are better satisfied and happier, if they are allowed to proceed with their usual occupations. It is perfectly obvious that interference with a schoolboy's activities or a man's business career or a woman's household duties entails hardship and anxiety not only for the

patient but for members of the immediate family. The wearing of medium weight, woolen underclothing and stockings, proper protection from snow and rain by rubbers, arctics, overcoats and raincoats, the avoidance of drafts or any exposure which will lead to chilly sensations, the shunning of family and friends ill with colds or infectious diseases, all seem directions almost too obvious to be worthy of mention; still these ought to be impressed upon the patient with a distinct warning that they must be adhered to without exception. If to these directions is added the warning that neither in the pursuit of pleasure nor of work should excesses be indulged in, and that a proper amount of rest should be obtained, not only at intervals, but every night, all the advice that can possibly help the patient to prevent a recurrence of his nephritis has been given. I believe that under such a regime the results have been equally good in cool as in warm climates, and the patients have been very much happier in their home surroundings and with their accustomed responsibilities.

The use of alcohol, not only in the treatment and prevention of acute nephritis but in all forms of Bright's disease, presents the same problems and may be discussed at this point. Alcohol does not damage the renal parenchyma; it is eliminated by the various emunctories as carbon dioxide and water which entail no strain upon the kidney. Alcohol taken in appropriate quantities will serve to stimulate a waning appetite, will give taste to a monotonous, low protein, high starch diet and will act as a food and as a protein sparer. It may, therefore, be prescribed without hesitation and in renal disorders even when patients are seriously ill; at times it is urgently indicated. The harmful effects ascribed to alcohol in Bright's disease, aside from the baseless tradition forbidding coffee, tobacco and alcohol

in all chronic diseases, are the lowered vitality and increased susceptibility of the patient to infections and consequently to acute nephritis when there has been an overindulgence in light wines, beer or hard liquor; alcohol in excess should, therefore, be absolutely forbidden; small, rational amounts as appetizers and nutriment are distinctly in order for many patients.

The Treatment of Subacute Diffuse Glomerular Nephritis

This form of nephritis, as previously mentioned, is comparatively rare. It is characterized clinically by progressive renal insufficiency terminating fatally within a comparatively brief period. This kidney lesion should not be confused with the subacute nephritis described in most textbooks, i.e., an intermediate stage indicating a prolongation of the acute stage which ultimately may become chronic. The only form of treatment of this condition, which may be considered as possibly affecting the kidneys, is the eradication of the focus of infection responsible for the kidney changes. In none of the cases, which I have seen thus far, has this or any other form of treatment been of the least benefit; the disease progresses irrespective of the therapy employed, and death occurs because of renal insufficiency.

The Treatment of Chronic Diffuse Glomerular Nephritis

There are two objectives in the treatment of this condition. (It must be understood that only those measures are being considered here which influence the pathological lesions in the kidney and not those which are intended to relieve edema, uremia, hypertension, etc.). In the first place, there are the procedures designed to eradicate foci of infection, especially

those harboring the hemolytic streptococcus. They are of great importance in preventing acute exacerbations and in doing away with a persistent source of irritation. This phase of the therapy has been described in the section on the treatment of acute diffuse glomerular nephritis under the captions of hygiene, climate and etiology; what has been said there as to acute nephritis applies equally to the persistent, i.e., chronic nephritis, and therefore need not be repeated at this point.

Secondly, the end products of protein catabolism are supposed to irritate the chronically inflamed kidney, and *dietary measures*, designed to limit the excretion of such substances, usually are instituted in a routine manner in the treatment of chronic diffuse glomerular nephritis. It is strikingly evident in taking up this question of the dietetic management of a persistent inflammatory reaction in the renal tissue that this form of Bright's disease should be considered as a group of problems and not merely as a renal disturbance. Thus the diet must be designed not solely to shield the kidney from strain incidental to the elimination of irritating end products of protein digestion, but the presence or absence of impaired renal function, of edema, of anemia, of hypertension and of uremia, each demand consideration in formulating a suitable dietary regime. All these indications must be balanced one against the other in each individual case, and it is the physician's function to choose a combination of foods to meet the demands of all these factors. At this moment only the diet that may affect the pathological processes in the glomeruli or tubules, that is, the nephritis, will be discussed; the other phases of this subject will be taken up in subsequent chapters.

Extensive research has been carried out to determine the *effect various foods may have upon the normal kidney*. It has

been a popular belief, not substantiated by accurate observations, that a high protein diet is responsible for damage to the kidney. We now have a number of publications, which show that a large amount of protein food in the form of meat may be taken without affecting the kidney. Lieb[68] showed how the explorer Stefansson lived for about nine years on a meat and fat diet and was in good physical condition in every way. Lieb[69], Tolstoy[70], and McClelland and Du Bois[71] report that two normal men, living for one year on an exclusive meat, fat diet, containing 100 to 140 grams of protein daily, showed no signs of renal damage. Furthermore, there are the reports of Thomas[72] that the high meat diet of the Eskimo exhibits no tendency to produce an increased blood pressure or a nephritis, and also those of Krogh and Krogh (quoted by Du Bois[73]) that the diet of the Greenland Eskimo, although it contains 280 grams of animal protein, 135 grams of fat and 54 grams of carbohydrates, causes no renal irritation. It has been claimed by some writers that these diets are not very much in excess of the protein intake indulged in by the average individual in so-called civilized countries. It may be well to recall at this point that Sherman[74] showed that an average of 42 grams of protein a day for a subject weighing 150 pounds was sufficient to maintain a nitrogen equilibrium, that is, a protein balance, between intake and output; this information was gathered from the data of 109 experiments by many observers. This does not mean that a protein balance cannot be obtained with widely different amounts of protein food, according as the diet is modified in various directions. However, it does mean that the average protein consumption is considerably less than that in the experiments of Du Bois and his collaborators or in the habitual diets of the Eskimos. My own conclusions, from the

study of several thousand persons while on their habitual diets, makes me believe that an intake of 60 grams of protein a day is rather a high than a low ration; it is exceedingly rare to find an individual, who is up and about and attending to his customary duties, who takes as much as 90 grams of protein a day. The conclusions, which it is desired to emphasize, is that *the amount of protein, which usually is consumed by persons living in the United States and Europe, is very distinctly within limits which will not bring about an injury to the normal kidneys.*

Newburgh, Lesses and Johnston[75] have published some observations on the nephropathic effect on man of a diet high in beef muscle and liver. Their experiment is worthy of note from many points of view, because it enables us to draw conclusions from a heroic effort which is not likely to be duplicated. The subject of this investigation was a laboratory worker who, for six months, consumed a diet containing 338 grams of protein, 271 of fat and 96 of carbohydrates, furnishing 4,177 calories daily, for a period of six months. The protein consumed daily was derived from the following sources:

Fresh beef liver	400 grams
Fresh veal round	300 grams
Fresh beef tenderloin	700 grams
Dry beef	100 grams

During the entire period of observation, no changes were noted in the retina, the blood pressure remained normal, and there were no subjective disturbances; there were noted an increased number of urinary casts and some albuminuria. After the high protein diet was discontinued, the casts and albumin disappeared completely within ten days. In interpreting this experiment recognition should be made of the fact that this subject took twice the number of calories necessary for main-

tenance and that the protein intake was anywhere from four to eight times the usual amount indulged in by persons living in a similar way. The kidney strain effected by this very excessive, almost inconceivably high, amount of protein food, consumed over a long period, is almost neligible; it is really surprising that all signs of irritation should have disappeared within a period of ten days. We are, therefore, justified in extending the conclusion drawn at the end of the last paragraph and *to believe that an amount of protein far in excess of that which is consumed usually by the average individual, will not injure the normal kidneys.*

The above investigations seem to establish the fact that any amount of protein food, which a normal person habitually consumes, will not produce a nephritis. The next step in this problem is the consideration of the effect of very excessive amounts of protein taken over long periods. It has proved too impracticable to carry out such observations in man; rabbit experiments of this type cannot be considered valid because the rabbit is an herbivorous animal. The rat has been chosen because the kind of food it eats is comparable to that consumed by man, furthermore, because a comparatively short period of study in a rat corresponds to many years of a human being's existence. In summary, *it has been found that the kidneys of rats fed on excessive protein rations may be normal, they may show hypertrophy, and they may show renal lesions similar to those of true glomerular nephritis.* It appears that the amount of protein food, the kind of protein food and the length of time for which the protein feeding is continued, all have an influence upon the type of response which the kidney manifests.

Hypertrophy of the kidney parenchyma is known to occur in man after unilateral nephrectomy or following the destruction

of a portion of the renal tissue from any cause. Thus, it is part of the pathological change which occurs in the functioning remnant of kidneys partially destroyed through inflammatory or arteriosclerotic processes, that is, in secondary or primary contracted kidneys. Such hypertrophies are compensatory in character. Experiments on rats show that hypertrophy of the kidney occurs in response to huge amounts of various forms of food. The feeding of urea will bring about either a slight hypertrophy or none at all (Osborne, Mendel, Park and Winternitz[76], Newburgh and Curtis[77]). The feeding of large amounts of protein food, both casein and meat, causes hypertrophy of the kidney, which may become evident within eight days. This hypertrophy is marked after feeding rats with considerable concentrations of casein, meat residue and gliadin (Osborne, Mendel, Park and Winternitz[76], Jackson and Riggs[78]). When the high protein diets are combined with unilateral nephrectomy, the hypertrophy of the remaining kidney is more marked; the experiments of Moise and Smith[79] show that with an 18 per cent. casein ration the kidneys hypertrophy 44 per cent., as measured by weight, within 20 days and with an 85 per cent. casein ration 123 per cent. within the same period. After 20 days there was no further enlargement of the kidney. Thus, we see that hypertrophy of the kidney takes place in response to physiological stimulation (Jackson and Riggs[78], Miller[80]) as well as to pathological ones, such as outlined above; this is noted in the experiments on rats, combining the effects of nephrectomy, a high protein diet and gestation, in which the renal hypertrophy, at times, was more than 200 per cent. (Parsons, Smith, Moise and Mendel[81]).

The conclusion, which we are justified in arriving at, is that *renal hypertrophy occurs whenever there is an increased demand*

put upon the kidney whether from natural or pathological causes; renal hypertrophy is, therefore, a normal response of the kidney tissue to increased demands for activity. We are not informed as to how well this renal tissue will maintain its integrity for a long period of time. In other words, can it continue its viability indefinitely, or is t prone to sclerosis or other changes at an early period as compared to normal kidney tissue?

Pathological changes in the kidney may be produced by an extremely high protein intake. Enough protein to effect such changes has never been consumed by man; the validity of this statement depends upon observations made on white rats. These results in rats, as has been especially stressed by Newburgh and Curtis[77], depend upon the concentration of the protein, its type and the duration of the feeding. Thus, casein, which has been investigated more thoroughly than any other kind of protein, in the experiments with white rats, will not cause kidney changes even though the casein is fed in concentrations as high as 76 per cent. and in periods up to one year (Kennedy[82], Reader and Drummond[83], Drummond, Crowden and Hill[84], Osborne, Mendel, Park and Winternitz[76] and Addis, Mackay and Mackay[85]). Newburgh and Curtis[77], by prolonging the duration of such casein diets up to 18 months, could produce degeneration of the tubules in their animals. Moise and Smith[79] were able to bring about both glomerular and tubular changes within 90 to 150 days in animals fed 85 per cent. casein after unilateral nephrectomy. Thus, it is proved *that both the duration of feeding and the amount of active kidney tissue remaining are factors that influence the degree of susceptibility of the renal parenchyma to damage through excretory products.*

Newburgh and Curtis[77] found also that beef muscle protein in concentrations of from 38 per cent. to 75 per cent., fed for

more than a year, caused a considerable degree of glomerular fibrosis resulting in the formation of a granular kidney; such changes were even more marked when liver instead of beef muscle proteins were fed. None of the rats on the liver diet survived a year. Moise and Smith[79] in their nephrectomized rats found similar glomerular changes with casein. These facts, combined with those mentioned previously when the effects of casein were discussed, point to the conclusion that not only the amount of protein but the kind of protein may influence the extent and type of renal lesion produced.

From all these experimental observations, certain facts would appear to stand out:

(1) *Any reasonable amount of protein food, or any amount of protein food that will be consumed habitually by a human being, will not damage a normal kidney nor cause it to hypertrophy.*

(2) *Very large amounts of protein food, that is, quantities which have never been eaten by man but will be devoured by white rats, may result in hypertrophy of the kidney and in renal lesions similar to those present in glomerular and tubular nephritis.*

(3) *The effects of the elimination of protein end products upon hypertrophied kidney tissue, and on kidney tissue which is the seat of an inflammatory lesion, are entirely separate problems and are to be taken up in the paragraphs that follow.*

From the point of view of the physician, who is prescribing a diet for the sufferer with chronic diffuse glomerular nephritis, there are three types of pathological change in such kidneys that should be considered. These are destruction, hypertrophy and inflammation. It is perfectly obvious that the renal parenchyma which has been destroyed or fibrosed will not be influenced by dietary measures, and this side of the problem, therefore, need not be discussed. There remains the question

of how we may influence the course of the hypertrophy and inflammation within the kidney by the regulation of the diet. Concerning these subjects, we have very scant knowledge.

Hypertrophy of the kidney in chronic diffuse glomerular nephritis occurs in the surviving renal parenchyma, when a considerable number of the kidney glomeruli and tubules have been destroyed and undergone fibrosis. Our knowledge of how such hypertrophied tissue reacts to the strain imposed upon it by excretion is very limited. The hypertrophy, which takes place in the remaining kidney after unilateral nephrectomy, apparently, does not predispose to disease, although the normal activities and diet of such patients are aintained. We can only venture the conclusion that *in chronic diffuse glomerular nephritis the hypertrophied renal elements are no more vulnerable than normal kidney tissue and need not, therefore, be considered as requiring dietary restriction.*

Squier and Newburgh[86] have made one of the few attempts to investigate the effect of protein foods upon the inflammatory processes existing in chronic nephritis. They used control periods of a low protein diet of 33 grams a day and then plunged into high protein diets of 100 to 175 grams a day. These investigators found that the high protein dietary produced an increased amount of albumin and red blood cells in the urine, was accompanied in some instances by the formation or increase of edema and resulted, at times, in an exacerbation of the retinitis; in the normal controls of this series, red blood cells were found in the urine, but there was no albuminuria. It may, therefore, be concluded that the subject of Bright's disease was more vulnerable than the normal individual not only as far as his kidney is concerned, but likewise in other respects, as evidenced by the exacerbations of the retinitis and

the appearance of the edema. There are two further points which are worthy of note in these observations. In the first place, the addition of salt to the diet aggravated both the hematuria and the albuminuria, and we may, therefore, believe that other substances besides proteins may act as irritants to a diseased kidney. In the second place, the appearance of red blood cells in the urine of normal individuals, when these large amounts of protein food were administered, indicates that possibly the diseased kidney is not very different from the uninjured organ.

Newburgh[87], in 1923, in summarizing his observations, came to the conclusion that great overindulgence in protein is a cause for chronic nephritis. I do not believe we have sufficient evidence on hand to be certain of this statement. I have given certain patients with albuminuria, both with and without signs of renal insufficiency, as evidenced by an increase in the blood urea nitrogen, considerable quantities of protein food for a number of years without noting any pathological changes in the kidney that might be ascribed to such a diet. It is well known that in the tubular lesions of the kidney large amounts of protein may be taken without causing the kidney any damage (Epstein Peters and Bulger[88], Barker and Kirk[89]). Not only is this true, but the renal lesions have been known to diminish in intensity, while such a diet was being consumed Furthermore, as previously discussed, there is a strong probability that in these cases not only are the tubules involved, but that the glomeruli are also the seat of disease.

This evidence and the facts given in previous paragraphs would point to the probability that, *although a high protein diet might increase albuminuria and red blood cells in the urine, yet, that this was not significant of any real pathological damage*

to the kidney. It has been pointed out not only by the authors mentioned above, but also by Du Bois[73] and Mosenthal and Richards[90], that it is not only desirable but also feasible to create a favorable nitrogen balance by a moderately high protein diet in cases of nephritis. There is another interesting side to this question, which may furnish food for thought to those who would advocate the lowest possible amount of protein food in chronic diffuse glomerular nephritis. This is the fact brought out by Barker and Kirk[89] that a continued lowering of the blood proteins results in a tubular nephritis, which ultimately involves the glomeruli as well and brings about a severe type of secondary contracted kidney. Thus, while there may be dangers to the kidney from a high protein diet, there are also those entailed by an excessively low protein ration.

Finally, it becomes necessary to consider the *effect of protein feeding upon the diminished amount of functioning kidney substance, the inevitable result of a persistent chronic diffuse glomerular nephritis.* The experiments on rats, that have been cited in some of the previous sections, show that, when only a remnant of renal parenchyma functions, this is much more prone to become the seat of an inflammatory reaction both in the glomeruli and tubules than if the kidneys remain intact. There are some clinical observations which indicate that the kidneys with diminished renal parenchyma do not necessarily become injured through the stress of compensatory effort to which the remnant of functionating tissue is subjected. This is well shown in the long lease of life sufferers with congenital polycystic kidneys exhibit even after their renal function is very much diminished, and the blood urea values are at a high level. In this connection the observation of O'Hare[91], that low renal function may be compatible with a longer period of life than is

usually expected, points to the fact that an accumulation of the urinary excretory products within the blood does not necessarily harm the kidneys, but that other insults are the real causes for the progressive destruction of the glomeruli. *We believe, therefore, that the injurious effect, which a moderately high protein diet may have upon the kidney with some impairment of renal function, has been exaggerated.*

A summary of the facts discussed in the previous pages would indicate that there is probably some irritation accruing to the kidney in chronic diffuse glomerular nephritis from the elimination of the end products of protein metabolism. This in itself, if unaccompanied by other influences productive of further progress in the renal lesions, would be a matter of small importance. However, if we yield to the impulse to save the kidney from as much strain as possible and advise the lowest conceivable protein diet for these patients, the result may be a lowered protein content of the blood entailing a renal lesion and edema; furthermore, secondary anemia, malnutrition and invalidism are very likely to develop and, in brief, the very purpose of the diet, namely, to render the patient comfortable and efficient and to prevent the progress of the renal lesion, will be nullified. Consequently, it would seem wise *never to allow these patients less than 40 grams of protein a day unless the renal function is so much curtailed that retention uremia is threatened;* further *special indications for feeding higher amounts of protein may be found in the presence of edema anemia, obesity or malnutrition.* In addition, there should be enough protein food to cover the loss of albumin in the urine so that the formula for the amount of protein administered would be approximately *40 grams of protein a day plus an amount of protein equal to the quantity of albumin lost in the urine.* While

such a diet is carried on, the patient must be watched especially for anemia, and if this should develop, an increase in the protein of the diet should be considered, if possible.

A convenient method of feeding such patients and measuring approximately the amount of protein in the food, may be gathered from the accompanying diet sheet which is modified from a list prepared by O'Hare. In this list every one of the portions in Group I contains approximately 4 grams of protein. The foods in Group II contain practically no protein and may be allowed in any amounts.

Care must be taken that the salt especially is restricted, because it has been shown that this substance will irritate a diseased kidney.

It must be understood that the points discussed above concern only the treatment of the lesions in the kidney and that other indications for therapy may present themselves in any case, according to the intensity of the signs and symptoms incident to renal insufficiency, edema, anemia, hypertension or uremia. These will be discussed in the proper sections.

Diet List Designed for Use in the Treatment of Bright's Disease

This diet list is modified from one published by James P. O'Hare. Each of the portions designated in Group I contains about 4 grams of protein; the foods in Group II contain only a negligible amount of protein.

Any combination of the foods listed below may be selected.
Foods not listed below must not be taken.
In Group I there is a restriction in the total amount.
A full portion in Group I counts 1.
In Group II the quantity of each is not restricted.
Your total score for the day should be .... portions of Group I.

Your total amount of fluid should be .... glasses or cups a day.
Use no spices. Directions for the use of salt:

GROUP I — EACH FULL PORTION COUNTS 1

	Full Portion		*Full Portion*
Bread — any kind	1 av. slice	Baked beans	1 tbsp.
Shredded wheat	1 biscuit	Lima beans	1½ tbsp.
Uneeda biscuit	5 crackers	Green peas	2 tbsp.
Oatmeal	2 tbsp.	Canned corn	2½ tbsp.
Boiled rice	3 tbsp.	Mushrooms	4 tbsp.
Cornmeal mush	4 tbsp.	Macaroni	4½ tbsp.
Cream of wheat	6 tbsp.		
Farina	6 tbsp.	Puddings except cornstarch or tapioca, see Group II)	1 helping
Hominy	6 tbsp.	Pie	1 helping
Milk, cream or buttermilk	½ glass	Cheese	1 tsp.
Egg	¾ egg	Custard	1 tbsp.
Fish or meat when cut to equal	1 tbsp.	Ice cream	1 tbsp.

GROUP II — NO RESTRICTIONS

Vegetables		*Fruits*		*Miscellaneous*	
Asparagus	Onions	Apples	Oranges	Candy	Cornstarch
Beets	Potatoes	Applesauce	Peaches	Honey	Tapioca
Broccoli	Pumpkin	Bananas	Pears	Maple syrup	Butter
Brussels sprouts	Rutabaga	Blueberries	Pineapple	Maple sugar	Lard
	Spinach	Dates	Plums	Sugar	Olive oil
Carrots	Squash	Figs	Prunes	Syrup	
Cauliflower	String beans	Grapes	Raspberries	Arrowroot — arrowroot biscuits	
Celery	Sweet potatoes	Grapefruit	Rhubard		
Cucumbers		Lemons	Strawberries		
Kohlrabi	Tomatoes	Muskmelon	Watermelon		
Lettuce	Turnips	Nectarines			

The Treatment of Focal Glomerular Nephritis

The treatment of focal glomerular nephritis, whether of the focal infectious or the focal embolic type, resolves itself into the control of the original infectious process to which the nephritis is secondary by the use of therapeutic measures appropriate to the particular disease. No other form of therapy will influence the pathological lesion in the kidney.

The Treatment of Tubular Nephritis

Cases of tubular nephritis are very similar in their renal histology but differ very markedly in their clinical symptomatology. At this point we shall discuss only the treatment of the tubular nephritis and not of the accompanying clinical symptoms.

The symptoms and signs associated with tubular nephritis usually are considered as being of much more importance than the pathological process. For instance, the anasarca of edematous tubular nephritis, the oliguria of bichloride of mercury poisoning and others, are justly regarded in this light by physicians; however, the treatment of these states will have to be taken up in the appropriate sections on edema, renal function, etc., and only measures that influence the kidney lesion itself will be considered here; this is in accordance with the conception of Bright's disease followed in this book.

The tubular lesions, it is generally believed, are the result of the excretion of some noxious material. We have seen above that the *albuminous form of tubular nephritis*, i.e., the febrile albuminuria, occurring during the course of nearly all infections, is negligible in its effect upon the kidneys and disappears very promptly when the primary disease has been cured. The same may be said of the second, more advanced stage of tubular nephritis, that is, the *hyaline degeneration;* this is found in severe or prolonged types of infection and also disappears very promptly when the bacterial or parasitic invasion responsible for it has been overcome.

The most severe type of tubular involvement, that is, *necrosis*, is also prone to heal, when the elimination of the poison responsible for it ceases. While necrosis in tubular

nephritis has been reported as complicating diphtheria, cholera, malaria, dysentery, sulphuric acid poisoning and other toxic states, the only clinical condition in which it really becomes important is the poisoning with bichloride of mercury. If the patient outlives the oliguria and survives the period of elimination of all the retained mercury, the kidney will again return to normal in both function and structure. It is the oliguria that usually brings about the fatal termination in these cases, and it is this diminished kidney function that demands particular attention in our therapy.

Scant attention is accorded these renal lesions, accompanying the various forms of tubular nephritis, for two reasons: first, because, in themselves, they have little influence upon the symptoms of the disease, except for the oliguria of bichloride of mercury poisoning, and second, because they are susceptible of no treatment save only cutting off the source of the noxious substances that on elimination irritate the kidneys. The latter is an easy conception to formulate and often an exceedingly difficult objective to reach.

On the other hand, the changes in the kidney in tubular nephritis are not without their significance and should not be neglected. They are indications that noxious materials are being produced within the body, and while they may be regarded as primarily of symptomatological importance, it would not be wise to disregard them even though they be looked upon only as signals of potentially harmful processes. Furthermore, it has been shown that in a persistent and severe necrotic form of nephritis the kidney may undergo secondary fibrotic degeneration and change into a secondary contracted kidney that, at a later period, may threaten life through renal insufficiency.

The Treatment of Special Forms of Tubular Nephritis

Finally there remains to be considered the treatment of the special forms of tubular nephritis, i.e., with lesions characterized by lipoid and amyloid infiltration. In these cases lipoid or amyloid material is formed as the result of certain constitutional changes and is deposited in the diseased kidney cells. It is perfectly apparent, therefore, that we must treat the original cause, responsible for the accumulation of these substances, and that any attempt to influence the kidney directly by other means is futile. *Amyloid changes* within the body, as is well-known, are caused by chronic suppurative or cachectic conditions, which are often impossible of eradication; however, attacking these holds out the only hope for cure of the amyloidosis not only in the kidney, but throughout the body.

The Treatment of Edematous Tubular Nephritis, Lipoid Nephrosis or Genuine Nephrosis

Although at this point it is desired to consider only the therapy that will ameliorate the pathological changes in the kidney, it is necessary when describing the treatment of the renal lesions of genuine or lipoid nephrosis, i.e., edematous tubular nephritis, to overstep these limits somewhat, because recent brilliant researches and theories have made it evident that the part which the kidney plays in this disease is extremely complex and admits of various interpretations. The cause for the edema, which is the outstanding clinical feature of edematous tubular nephritis, is the lowered protein content of the blood serum. This idea was promulgated originally by Epstein[4], as previously mentioned, and his contentions have been completely substantiated, especially by the animal experi-

ments of Leiter[92], of Frisch, Mendel and Peters[93], and of Barker and Kirk[89]. Epstein[4] elaborated his original conception of the pathological physiology of lipoid nephrosis by ascribing the cause of this disease to the diminution of protein in the blood serum; that is, the changes in the kidneys were believed to be the result of the lowered albumin content and reversed albumin: globulin ratio of the blood. Barker and Kirk[89] were able to demonstrate that this actually occurred; by removing the serum proteins in dogs through "plasmapheresis", they not only produced edema in these animals but also, and this is the important point, found that tubular lesions resulted in the kidneys when the proteins in the blood serum were markedly lowered.

The diminution of the albumin in the blood serum was demonstrated to be the keystone upon which the formation of the edema depended. Barker and Kirk[89] showed that when the albumin dropped below 1 gram per 100 c.c. of blood, edema resulted in human patients as well as in experimental animals; furthermore, the intensity of the edema was directly proportional to the degree to which the blood albumin was lowered; when the albumin was above 1 per cent. in the blood the edema promptly disappeared. In my experience, the crucial level of albumin in the blood is considerably higher than 1 per cent. In our clinic we have witnessed marked edema when the albumin content of the blood was as high as 2.5 per cent. The changes in the tubules of the kidney presumably fluctuate in much the same way and in response to the same cause as the edema. Consequently it would seem that the kidney lesions, as far as the damage to the tubules was concerned, could be controlled by maintaining the albumin in the blood at a normal level. These conclusions are substantiated by an isolated but

extremely fortunate observation of Jungmann[94], who obtained a biopsy of the kidney in a typical case of nephrosis and found it anatomically intact, although later on, at autopsy, the typical lesions of edematous tubular nephritis were revealed. The finding of Wolbach and Blackfan[32] that these kidney lesions are cyclical in their progress, alternately healing and recurring, must be considered as a possible explanation of Jungmann's report. In summary the sequence of the essential features of lipoid nephrosis may be pictured as follows:

1. Cause?
   ↓
2. Albuminuria
   ↓
3. Lowered albumin content of the blood
   ↙ ↘
4. Edema Tubular nephritis

If, as is our purpose at this moment, we desire to institute treatment that will cure the kidney lesion, tubular nephritis, it is clear that we must do away with the primary cause, that is, the albuminuria. Here an immediate difficulty presents itself, for what abnormal state brings on the albuminuria is not known; Epstein[4] ascribes it to some change in the character of the serum proteins that lends them the character of foreign proteins and thus endows them with the quality of permeating the glomerular capillaries and escaping into the urine; Löhlein[23], Bell[45] and Elwyn[46], as previously mentioned, believe that the primary pathological lesions develop in the glomeruli; this conception is substantiated by Barker and Kirk[89], who have noted that edematous tubular nephritis may follow upon acute diffuse glomerular nephritis; translating these conceptions into terms of etiological significance, they would point to a focus of infection harboring hemolytic streptoccoci; finally, there is the

idea advanced by Clausen[95] that staphylococci, either albus or aureus, growing in the paranasal sinuses, are responsible for the albuminuria. A survey of these theories crystallizes the therapeutic possibilities that may be followed in an attempt to stem the albuminuria. They may be summarized in this way:

1. There are no means known at present by which the theoretical change of serum proteins, described by Epstein[4], can be prevented.

2. Glomerular lesions in the kidney or the sequelæ of acute diffuse glomerular nephritis should be given the same consideration as acute diffuse glomerular nephritis, and special attention should be devoted to the eradication of infections due to the hemolytic streptococcus.

3. Staphylococcus infections of the paranasal sinuses must be sought for and eliminated.

Whether any or all of these methods of treatment will prove successful remains to be determined.

The accepted treatment, at the moment, of edematous tubular nephritis consists in attempts to afford symptomatic relief to the lowered albumin content of the blood. Such a method of procedure will not only heal the kidney lesion but also do away with the edema, as indicated in the previous scheme. However, the albuminuria and its train of symptoms will recur, since the cause of the albuminuria has not been removed. These matters will be taken up in full detail under the treatment of edema, but a few points may be mentioned here. Three means that are commonly resorted to are the administration of large amounts of protein food, thyroid medication and transfusions of blood. The injection of human blood, even in large amounts frequently repeated, has in my experience not been effective in ameliorating either the al-

buminuria or the edema. The use of thyroid substances may relieve the edema temporarily but has no demonstrable effect upon the kidney lesion. The feeding of large amounts of protein is definitely effective provided a sufficient amount can be administered to balance the loss of serum albumin in the urine. Peters and Bulger[88], and Barker and Kirk[89] believe the condition may be controlled if a positive nitrogen or protein balance is obtained. Barker and Kirk[89] were able to accomplish this, provided the albuminuria did not exceed 10 grams per day.

Peters and Bulger[88], by resorting to a high carbohydrate and fat diet were able to obtain a favorable nitrogen balance on diets containing 0.5 to 0.7 grams of protein per kilogram a day; judging from the protocols, they fed their patients between 50 and 100 grams of protein a day, in the majority of instances the amount of protein used being in the neighborhood of about 75 grams. These are protein intakes within the average normal range, and it is gratifying to know that they could achieve such favorable results through the help of fats and carbohydrates fed in liberal amounts.

Epstein[4] advocates much higher protein diets, and he believes in restricting the carbohydrates and the fats. The carbohydrates are limited because they favor the production of edema, and the fats are held as low as possible in the diet because they are supposed to influence the high blood cholesterol adversely. Most clinicians believe that the rôle of the carbohydrates in the production of edema is not very important, and the opinion is rather gaining ground that the high blood cholesterol is the result of inanition and would in fact be relieved, to a certain extent, by a high fat diet. The diet advocated by Epstein[4] is as follows:

DIET EMPLOYED BY EPSTEIN

	Daily Amount
Food Value	1280 to 2500 calories
Proteins	120 to 240 grams
Fats (unavoidable)	20 to 40 grams
Carbohydrates	150 to 300 grams

Articles Used

Lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea and cocoa.

It would seem that, if a positive protein balance can be obtained by means of the diets advocated by Peters and Bulger[88], that this would be the preferable form of dietetic therapy.

The Treatment of Vascular Nephritis

Vascular nephritis, or nephrosclerosis, is a kidney condition due to a disease of the renal arteries and arterioles occurring as a complication of hypertension or as a part of a generalized arteriosclerosis. It is self-evident that the pathology of the kidney cannot be influenced by local treatment, but may be affected by measures which control the high blood pressure or the generalized arteriosclerotic process. Lead may be responsible also for this disease of the kidneys; the report of L. J. Nye[96] concerning the "extraordinary incidence of chronic nephritis in young people of Queensland" is exceedingly interesting. He believes that poisoning by white lead contained in paint is the cause for the prevalence of this form of nephritis in parts of Australia.

BIBLIOGRAPHY

1. CUSHNY, A. R.: The Secretion of Urine, Second Edition, 1926.
2. ANDREWS, E., THOMAS, W. A. and WELKER, W. F.: Albuminuria in the mechanism of detoxification, Arch. Int. Med., **43**: 139, 1929.

3. Andrews, E. and Thomas, W. A.: The origin of urinary proteins, Jour. Am. Med. Assoc., **90**: 539, 1928.
4. Epstein, A. A.: Concerning the causation of edema in chronic parenchymatous nephritis: method for its alleviation, Am. Jour. Med. Sc., **154**: 638, 1917. Thyroid therapy and thyroid tolerance in chronic nephrosis, Jour. Am. Med. Assoc., **87**: 913, 1926. Über Diabetes Albuminuricus, die sogenannte chronische Nephrose, Arch. f. Verdauungskr., **44**: 31, 1928.
5. Hiller, A., McIntosh, J. F. and Van Slyke, D. D.: The excretion of albumin and globulin in nephritis, Jour. Clin. Invest., **4**: 235, 1927.
6. Heubner, O.: Die chronischen Albuminurien im Kindesalter, Ergebn. d. inn. Med. u. Kinderh., **2**: 567, 1908.
7. Jehle, L.: Die Albuminurie, Ergebn. d. inn. Med. u. Kinderh., **12**: 808, 1913.
8. Erlanger, J. and Hooker, D. R.: An experimental study of blood pressure and of pulse pressure in man, Johns Hopkins Hosp. Reports, **12**: 145, 1904.
9. Ashburn, P. M.: An epidemic of albuminuria, Jour. Am. Med. Assoc., **90**: 35, 1928.
10. Ashe, B. I.: The hemoglobin percentage and the red blood cell count in Bright's disease, myocardial insufficiency and hypertension, Arch. Int. Med., **44**: 506, 1929.
11. Linder, G. C., Lundsgaard, C. and Van Slyke, D. D.: The concentration of the plasma proteins in nephritis, Jour. Exp. Med., **39**: 887, 1924.
12. Hiller, A., Linder, G. C., Lundsgaard, C. and Van Slyke, D. D.: Fat metabolism in nephritis, Jour. Exp. Med., **39**: 931, 1924.
13. Addis, T.: A clinical classification of Bright's disease, Jour. Am. Med. Assoc., **85**: 163, 1925.
14. Addis, T.: Renal failure casts, Jour. Am. Med. Assoc., **84**: 1013, 1925.
15. Fahr, T.: Handbuch der Speziellen Pathologischen Anatomie und Histologie, Henke, F. und Lubarsch, **6**: 1925.
16. Volhard, F. and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, 1914.
17. Elwyn, H.: Nephritis, New York, 1926.
18. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, 1930.
19. Christian, H. A.: Classification of chronic nephritis, Jour. Am. Med. Assoc., **85**: 1701, 1925.
20. Müller, F.: Morbus Brightii, Verhandl. der Deutsch. Patholog. Gesellschaft, 64, 1905.

21. Herxheimer, G.: Nierenstudien II. Über Anfangstadien der Glomerulo-nephritis, Beitr. z. pathol. Anat. u. z. allg. Pathol., **64**: 454, 1917–18.
22. Welch, W. H.: Discussion on tubular nephritis, Trans. Assoc. Am. Physicians, **44**: 119, 1929.
23. Löhlein, M.: Über die entzündlichen Veränderungen der Glomeruli der menschlichen Niere, Arbeit. aus d. patholog. Institut zu Leipzig, **1**: 1, 1907.
24. Baehr, G. and Ritter, S. A.: The arterial supply of the kidney in nephritis: its relation to the clinical picture, Arch. Path., **7**: 458, 1929.
25. O'Hare, J. P. and Walker, W. G.: Hemorrhagic nephritis, Atlantic Med. Jour., **27**: 280, 1924.
25 (*a*). Baehr, G.: A benign and curable form of haemorrhagic nephritis, Jour. Am. Med. Assoc., **86**: 1001, 1926.
26. Munk, F.: Nierenerkrankungen, Berlin, 1925.
27. Volhard, F.: Die Doppelseitigen Hämatogenen Nierenerkrankungen, Berlin, 1918.
28. Löhlein, M.: Über hämorrhagische Nierenaffektionen bei chronisher ulzeröser Endocarditis, Med. Klin., **6**: 375, 1910.
29. Baehr, G.: Glomerular lesions of subacute bacterial endocarditis, Jour. Exp. Med., **15**: 330, 1912; Glomerular lesions of subacute bacterial endocarditis, Am. Jour. Med. Sc., **144**: 327, 1912.
30. Baehr, G. and Lande, H.: Glomerulonephritis as a complication of subacute streptococcus endocarditis, Jour. Am. Med. Assoc., **75**: 789, 1920.

Baehr, G.: The significance of the embolic glomerular lesions of subacute streptococcus endocarditis, Arch. Int. Med., **27**: 262, 1931.

31. Christian, H. A.: Nephrosis: a critique, Jour. Am. Med. Assoc., **93**: 23, 1929.
32. Wolbach, S. B. and Blackfan, K. D.: Clinical and pathological studies on tubular nephritis (nephrosis), Trans. Assoc. Am. Physicians, **44**: 77, 1929.
33. Hunter, W. C.: Regeneration of tubular epithelium in human kidney following injury by mercuric chloride, Ann. Int. Med., **1**: 463, 1928.
34. Lewis, D. S. and Rivers, T. M.: Chemical studies on a case of bichloride poisoning, Bull. Johns Hopkins Hosp., **27**: 193, 1916.
35. Killian, J. A.: Note on the blood chlorides in mercuric chloride nephrosis, Jour. Lab. and Clin. Med., **7**: 129, 1921.
36. Trusler, H. M., Fisher, W. S. and Richardson, C. L.: Chemical changes in the blood in mercuric chloride poisoning, Arch. Int. Med., **41**: 234, 1928.

37. Richards, A. N.: Methods and Results of Direct Investigations of the Functions of the Kidney, Baltimore, 1929.
38. Janeway, T. C.: Nephritic hypertension: clinical and experimental studies, Am. Jour. Med. Sc., **155**: 625, 1913.
39. Rosenberg, M.: Die Klinik der Nierenkrankheiten, Berlin, 1927.
40. Aub, J. C. and Du Bois, E. F.: The respiratory metabolism in nephritis, Arch. Int. Med., **19**: 865, 1917.
41. Murphy, F. D. and Warfield, L. M.: Lipoid nephrosis, Arch. Int. Med., **38**: 449, 1926.
42. Davison, W. C. and Salinger, R.: Tubular nephritis (nephrosis) in children and its relationship to other forms of nephritis, Bull. Johns Hopkins Hosp., **41**: 329, 1927.
43. Mackay, E. M. and Johnston, C.: Lipoid nephrosis, Arch. Int. Med., **45**: 734, 1930.
44. Kaufmann, J. and Mason, E.: Nephrosis, Arch. Int. Med., **35**: 561, 1925.
45. Bell, E. T.: Lipoid nephrosis, Am. Jour. Path., **5**: 587, 1929.
46. Elwyn, H.: The pathogenesis of lipoid nephrosis, Arch. Int. Med., **38**: 346, 1926.
47. Shapiro, P. F.: Lipoid nephrosis: pathology, genesis and relation to amyloidosis, Arch. Int. Med., **46**: 137, 1930.
48. Alter, N. M.: The so-called "lipoid nephrosis," Arch. Path., **7**: 1122, 1929.
49. Rachmilewitz, M.: Hypercholesteremia associated with hepatosplenomegaly and nephrosis, Jour. Am. Med. Assoc., **93**: 604, 1929.
50. Keith, N. M., Wagener, H. P. and Kernohan, J. W.: The syndrome of malignant hypertension, Arch. Int. Med., **41**: 141, 1928.
51. Murphy, F. D. and Grill, J.: So-called malignant hypertension, Arch. Int. Med., **46**: 75, 1930.
52. Klemperer, P. and Otani, S.: Studies on "malignant sclerosis" of the kidneys (Fahr), Arch. Path., **8**: 559, 1929.
53. Herxheimer, G.: Ueber Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat., **251**: 709, 1924.
54. Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. allg. Path. u. path. Anat., **63**: 570, 1917.
55. Kaufmann, E.: Pathology, Philadelphia, Blakiston's Son & Co., 1929.
56. Bell, E. T. and Clawson, B. J.: Primary (essential) hypertension, Arch. Path., **5**: 939, 1928.
57. Oppenheimer, B. S. and Fishberg, A. M.: Hypertensive encephalopathy, Arch. Int. Med., **41**: 264, 1928.

58. Cohen, M.: Significance of pathologic changes in fundus, Jour. Am. Med. Assoc., **78**: 1694, 1922.
59. Brown, A. L: The ocular fundus in acute toxemias, Jour. Am. Med. Assoc., **89**: 174, 1927.
60. Leber, T.: in Saemisch und Elsching, Handbuch der gesamten Augenheilkunde, 2nd edition, **7**: 1319, 1916.
61. Longcope, W. T.: The pathogenesis of glomerular nephritis, Bull. Johns Hopkins Hosp., **45**: 335, 1929.
62. Lichtwitz, L.: Praxis der Nierenkrankheiten, 2d ed., Berlin, 1925.
63. Levy, I. J.: The cardiac response in acute diffuse glomerulonephritis, Am. Heart Jour., **5**: 277, 1930.
64. Christian, H. A.: Some studies of a diuretic (theocin), Arch. Int. Med., **18**: 626, 1916. Some observations on the use of diuretics in nephritis, Canad. Pract. and Rev., **42**: 269, 1917.
65. Harrison, R.: A contribution to the study of some forms of albuminuria associated with kidney tension and their treatment, Lancet, **1**: 18, 1896.
66. Edebohls, G. M.: Surgical Treatment of Bright's disease, New York, 1904.
67. Pospischill, D. and Weiss, F.: Ueber Scharlach, Berlin, 1911.
68. Lieb, C. W.: Effect of exclusive, long-continued meat diet, based on history, experience and clinical survey of Vilhjalmur Stefansson, arctic explorer, Jour. Am. Med. Assoc., **87**: 25, 1926.
69. Lieb, C. W.: The effects on human beings of 12 months' exclusive meat diet, based on extensive clinical and laboratory studies on two arctic explorers living under average conditions in a New York climate, Jour. Am. Med. Assoc., **93**: 20, 1929.
70. Tolstoi, E.: Effect of exclusive meat diet on chemical constituents of the blood, Jour. Biol. Chem., **83**: 753, 1929.
71. McClellan, W. S. and Du Bois, E. F.: Clinical calorimetry. Prolonged meat diets with a study of kidney function and ketosis, Jour. Biol. Chem., **87**: 651, 1930.
72. Thomas, W. A.: Health of carnivorous race; study of Eskimo, Jour. Am. Med. Assoc., **88**: 1559, 1927.
73. Du Bois, E. F.: Control of protein in the diet, Jour. Am. Dietet. Assoc., **4**: 53, 1928.
74. Sherman, H. C.: Protein requirement of maintenance in man and the nutritive efficiency of bread protein, Jour. Biol. Chem., **41**: 97, 1920.
75. Newburgh, L. H., Lesses, M. F. and Johnston, M. W.: The nephropathic effect in man of a diet high in beef and muscle, Am. Jour. Med. Sc., **179**: 305, 1930.

76. Osborne, T. B., Mendel, L. B., Park, E. A. and Winternitz, M. C.: Physiological effects of diets unusually rich in protein or inorganic salts, Jour. Biol. Chem., **71**: 317, 1927.
77. Newburgh, L. H. and Curtis, A. C.: Production of renal injury in the white rat by the protein of the diet: dependence of the injury on the duration of feeding and on the amount and kind of protein, Arch. Int. Med., **42**: 801, 1928.
78. Jackson, H., Jr. and Riggs, M. D.: The effect of high protein diets on the kidneys of rats, Jour. Biol. Chem., **67**: 101, 1926.
79. Moise, T. S. and Smith, A. H.: The effect of high protein diet on the kidneys, Arch. Path., **4**: 530, 1927.
80. Miller, A. J.: The influence of high protein diet on the kidneys, Jour. Exp. Med., **42**: 897, 1925.
81. Parsons, H. T., Smith, A. H., Moise, T. X. and Mendel, L. B.: Diet and tissue growth, Arch. Path., **10**: 1, 1930.
82. Kennedy, W. P.: Reproduction and diet in rat, Quart. Jour. Exp. Physiol., **16**: 281, 1926.
83. Reader, V. B. and Drummond, J. C.: Further observations on nutrition with diets rich in protein, Jour. Physiol., **59**: 472, 1925.
84. Drummond, J. C., Crowden, G. P. and Hill, E. L. G.: Nutrition on high protein dietaries, Jour. Physiol., **56**: 413, 1922.
85. Addis, T., MacKay, E. M. and MacKay, L. L.: The effect on the kidney of the long-continued administration of diets containing an excess of certain food elements. I. Excess of protein and cystine, Jour. Biol. Chem., **71**: 139, 1926.
86. Squier, T. L. and Newburgh, L. H.: Renal irritation in man from high protein diet, Arch. Int. Med., **28**: 1, 1921.
87. Newburgh, L. H.: The etiology of nephritis, Medicine, **2**: 77, 1923.
88. Peters, J. P. and Bulger, H. A.: The relation of albuminuria to protein requirements in acute diffuse nephritis, Arch. Int. Med., **37**: 153, 1926.
89. Barker, M. H. and Kirk, E. J.: Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, Arch. Int. Med., **45**: 319, 1930.
90. Mosenthal, H. O. and Richards, A. E.: Interpretation of a positive nitrogen balance in nephritis, Arch. Int. Med., **17**: 329, 1916.
91. O'Hare, J. P.: Compatibility of long life with low renal function, Jour. Am. Med. Assoc., **73**: 248, 1919.
92. Leiter, L.: Experimental edema, Proc. Soc. Exper. Biol. and Med., **26**: 173, 1928.
93. Frisch, R. A., Mendel, L. B. and Peters, J. P.: The production

of edema and serum protein deficiency in white rats by low protein diets, Jour. Biol. Chem., **84**: 167, 1929.

94. JUNGMANN: Discussion and case report, Deutsche. med. Wchnschr., **54**: 41, 1928.
95. CLAUSEN, S. W.: Parenchymatous nephritis; infection of paranasal sinuses as etiology, Am. Jour. Dis. Child., **29**: 752, 1925.
96. NYE, L. J.: An investigation of the extraordinary incidence of chronic nephritis in young people in Queensland, Med. Jour. Australia, **2**: 145, 1929.

CHAPTER XII

RENAL FUNCTION IN BRIGHT'S DISEASE

(Diagnosis, Signs, Symptoms and Treatment of Disturbances of Renal Function in Bright's Disease)

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The Elimination of Urine by the Normal Kidney

Much light has been shed upon the physiology of the kidney by researches of the last few years, notably those of A. N. Richards[1] and his associates. As a result of this work, certain features of the theories of Ludwig, Heidenhain, Cushny and others may be accepted as proved, and our conception of the formation of urine is established much more securely than it has been in the past. Although this newly acquired knowledge covers only a portion of the kidney's activities (notably the elimination of water, sodium chloride, sugar and urea; that of many other substances having not yet been worked out), it seems very much worth while to attempt a correlation of our clinical and experimental facts and thus try to achieve a pathological-physiological viewpoint in place of the prevalent empirical one in the clinical study of kidney function.

The present exposition of renal physiology is made largely from the articles by A. N. Richards[1] and E. K. Marshall, Jr.[2], and for detailed references these papers should be consulted. A. N. Richards and his associates have been successful in tapping the glomerular capsule in the kidney of a living frog by means of extremely fine capillary pipettes. This wonderful achievement has definitely established the fact that the fluid portion of the urine originates in the glomerulus. This glomerular fluid contains chloride, sugar and urea, whereas the bladder

urine may contain no chloride or sugar. From these observations it may be concluded that the glomerular fluid is a filtrate from the blood.

The concentration of chloride and urea in the glomerular urine may be greater than that in the plasma. Concerning the possibility that these findings indicate a process of secretion by the glomerulus rather than one of filtration, Richards says: 'It may be suggested that these figures indicate a glomerular secretion'. I do not think that this is the case. They rather show the necessity of a further scrupulous investigation of the fashion in which a physical process may be modified when it takes place through the living walls of tubes of capillary size." For the present, therefore, we may consider the formation of glomerular urine as being a filtration process modified, to a certain extent, by the glomerular capillaries and capsule.

Glomerular filtration takes place only when the blood is flowing through the capillaries of the glomerulus. It has been shown by Richards and Plant in a series of experiments, which have been verified subsequently, that the glomerular output is directly proportional to the pressure in the glomerular capillaries and that this factor alone, and not the volume of circulating blood, controls the quantity of urine formed. A systolic blood pressure of 35 to 50 millimeters of mercury is necessary for the production of urine. I have seen one case which, for at least 24 hours, was secreting urine with a systolic pressure varying between 34 and 39 millimeters of mercury.

If the concentration of the colloids in the plasma is reduced by dilution or otherwise, formation of urine will take place at a much lower pressure in the glomerular capillaries than when a normal osmotic tension exists within the blood. Partial occlu-

sion of a renal vein, which must raise the pressure within the glomeruli, leads to a diminution instead of an increase in the rate of urine formation. This, however, results in such a concentration of blood, and hence of colloids, in the glomeruli that effective filtration obviously is not increased but diminished. Richards and Plant explained this matter by showing that, when the volume flow of blood through the kidney was kept constant, partial occlusion of the renal vein resulted in the expected rate of urine formation.

The circulation within the glomeruli is so arranged that there is complete control of the blood pressure within the glomerular capillaries independent of the general circulation. In this respect they differ markedly from other capillaries. In the glomerulus a single arteriole, the vas afferens, breaks abruptly into a number of capillaries, thus increasing the cross-section of the vascular bed many times. Within the glomerulus, the capillaries reassemble into the efferent vessel, smaller in diameter than the afferent, whereas in other capillary systems the efferent veins are much larger than the afferent arteries and have no power of limiting the outflow of blood from the capillary area as do the efferent arterioles in the glomeruli. This peculiar structure makes the control of the blood pressure within the glomerulus independent of the general arterial pressure. The general arterial pressure, as far as the kidney is concerned, serves only as a potential source of energy which the glomeruli may draw upon by their own arterial control. The general blood pressure and the glomerular blood pressure, therefore, are not necessarily directly proportional to one another.

Direct observations of the glomeruli in the frog by Richards and Schmidt reveal that all of the glomeruli are not functioning

at the same time. The importance of this and other experiments may be realized from the following figures which apply to the rabbit and, presumably, to most mammalian kidneys. Under control conditions 50 to 85 per cent. of the glomeruli receive blood. When a diuretic such as caffeine or sodium chloride was given, 95 to 100 per cent. of the glomeruli became active. If vaso-constriction was produced by adrenalin or other means, the number of glomeruli receiving blood could be diminished at will to 40, 30, 20, 10 or 5 per cent. Thus it may be seen that according to existing stimuli, the number of active glomeruli may vary from very few to a great many.

The vascular control of the kidney, and consequently the kidney function, to a certain extent at least, rests with the individual glomeruli and is not entirely a matter of the whole kidney acting as a unit. This subdivision of control of the circulation is carried even further inasmuch as individual capillaries within the glomeruli become devoid of blood, while others within the same glomerulus maintain their circulation.

Every organ in the body, apparently, has its period of activity and rest; the systole and diastole of the heart may be considered as the best known example of this fact. The kidney is no exception to the rule, as has been shown in a series of difficult but successful experiments. The kidney with a diminished number of glomeruli must pay certain penalties. In such cases, as in advanced chronic nephritis, all of the remaining glomeruli, presumably, are constantly working at their maximal capacity under the diuretic stimulus of accumulated urea and other substances. This may account for the hypertrophy of the individual glomeruli and may be responsible for the evidence of fatigue that occurs in these kidneys or in any kidney that is being overloaded.

The function of the tubules must be, in part at least, to reabsorb water, salt and sugar from the glomerular urine. This is indicated by the fact observed by Richards that the glomerular urine contains salt and glucose, while the bladder urine may contain neither of these substances. The question of the activity of the tubules in relation to urea is somewhat more complex. It is certain that the concentration of urea in the urine is likely to be considerably higher than it is in the plasma. It may, therefore, be that action of the tubules concentrates urea simply by absorbing water, and it may be that urea is reabsorbed in the tubules but not as extensively as is salt. On the other hand, there is the possibility, which Marshall discusses at length without arriving at any final conclusion, that urea is excreted by the tubules. A very much higher concentration of urea than of salt in the urine occurs constantly in certain conditions (passive congestion, acute nephritis). It would be an easy matter either to explain this discrepancy on the basis of selective reabsorption of salt and water by the tubules, or, to attribute this variation to excretion of urea by the tubules; consequently, a definite answer cannot be given to this question except in so far that we must recognize that the behavior of the tubules in regard to urea and to salt is widely different.

The salient facts concerning the elimination of urine may be summarized as follows:

Glomerulus:

Elimination by physical filtration, possibly modified by the vital qualities of the cellular membranes.

Quantity of fluid eliminated by each glomerulus directly proportional to the blood pressure within the glomerulus; this blood pressure controlled by afferent and efferent glo-

merular arterioles independently of general arterial pressure.

Activity of glomeruli intermittent; usually 50 to 85 per cent. active; 100 per cent. activated by diuretics.

Tubule:

Reabsorption of water, salt and sugar.

Height of specific gravity directly proportional to amount of water reabsorbed.

Elimination of urea (?)

Urine:

Protein free.

Sugar free.

Varying concentration (specific gravity).

On the basis of the foregoing it is possible to offer explanations of several disturbances of renal function, and to interpret more satisfactorily than has been possible hitherto the phenomena of specific gravity and of quantity of urine eliminated. There are two functional anomalies, whose pathological physiology is cleared up, to a certain extent at least, by our present understanding of kidney activity. These are Renal Glycosuria and Diabetes Insipidus.

Renal Glycosuria

Renal glycosuria has, for many years, been ascribed to a deficient renal threshold. In all persons glucose is found in the glomerular urine, while the blood sugar is at a normal level; the sugar is abstracted from this urine in the tubules before it passes into the bladder. Granting this, it seems probable that in cases of renal glycosuria, where the urine contains glucose, although the blood sugar is not elevated, the tubules are at fault, and that it is their inability to reabsorb the glucose which

is responsible for the appearance of sugar in the urine. Consequently, the conception of a faulty renal threshold should be abandoned for one of impaired tubular function as an explanation of renal glycosuria. In observing cases of renal glycosuria, one sees that they may be roughly divided into two classes; first, those in which no abnormality beyond the functional disturbance mentioned above can be detected, and, second, those cases of acute and chronic nephritis which, together with the evidence of kidney disease, exhibit also traces of sugar in the urine with a normal blood sugar (Table 34). Such cases of

	Fasting	After 100 grams of glucose							
		15 min.	30 min.	45 min.	1 hour	1 hour 30 m.	2 hours	3 hours	4 hours
Blood Sugar %....	.10	.15	.18	.23	.26	.26	.23	.10	.07
Urine Glucose %...	.13	.13	.37	.80	1.61	3.33	2.00	1.11	.33

TABLE 34. — *Renal Glycosuria* — A case of severe nephritis (phenolsulphonephthalein excretion 22%; blood urea N 35 mg. per 100 c.c.). Sugar appears in the urine when the blood sugar is 100 mg. or less. This case serves to show that in nephritis with renal insufficiency the conception that an increased "renal threshold" exists, is not correct. Renal glycosuria is very probably due to defective tubular function, that is, a lack of reabsorption of the sugar, which is always present in the glomerular filtrate, but usually absent in the bladder urine.

Bright's disease show a parallelism between tubular involvement and tubular function, while the former show a change in function without a corresponding anatomical lesion. The cases of nephritis exhibiting this change are not very common, and yet, they are not rare. In my experience, cases of acute nephritis in children frequently show this condition, whereas it is not so often found in adults with acute nephritis; in advanced chronic nephritis a renal glycosuria is frequently present. These facts show conclusively that the belief that a high renal

threshold to glucose is responsible for the elevated blood sugar characteristic of nephritis, is not correct.

Diabetes Insipidus

Diabetes insipidus may be accounted for in a number of ways. Either there is deficient absorption of fluid by the tubules, or there is an enormous glomerular diuresis and because of the rapidity of flow over the tubular lining reabsorption is impossible; it is, of course, conceivable that both of these factors may be acting at the same time. It is generally recognized that the disturbances, characteristic of diabetes insipidus, are controlled by the mid-brain, or the posterior lobe of the pituitary gland, or both acting in unison. How these influences act upon the kidney, whether directly upon the glomeruli or tubules, or indirectly by changing the composition of the blood, remains to be seen. However, taking all of the available evidence into consideration, which it is impossible to rehearse at this point, it would seem that here, as in renal glycosuria, we may have a disturbance of tubular function, which manifests itself in the inability of the kidney to reabsorb water.

Methods of Testing Renal Function in Bright's Disease

Dye Tests

The Phthalein Test. — It is difficult to believe that prior to 1912 there was no adequate clinical test available to determine the status of kidney function. The world owes a great debt to Rowntree and Geraghty[3] for the "phthalein test". This method still is very satisfactory and serves the purpose for the physician and the hospital whose laboratory equipment and

facilities are limited, where quick results are desired, or when a check-up on other tests of renal function becomes necessary.

The phthalein test, or the "red test", or the "PSP test", is carried out as follows: About one-half hour before the drug is injected 400 c.c. of water are given. One c.c. of a specially prepared solution containing 6 mg. of phenolsulphonephthalein is injected intramuscularly, preferably in the lumbar muscles. At the end of two hours and ten minutes (ten minutes to allow for absorption and two hours for excretion) the urine is collected. It is made decidedly alkaline with a sodium hydroxid solution (10 to 25 per cent.) diluted to one liter and the percentage of phthalein excreted is determined by comparison with the standard in a suitable colorimeter. There are many variations from this technic which may be employed according to various indications or opinions.

Sub-cutaneous injections yield exceedingly unsatisfactory results. Under these conditions the dye seems not to be absorbed as it should be, and low readings that can be accounted for in no other way may be found. Consequently, the injection of the dye should not be relegated to an inexperienced and improperly instructed technician. The best results are obtained if the material is given via the lumbar muscles; there is always an element of uncertainty in regard to its absorption, if other sites are utilized. Intravenous administrations may be employed. If this is done, the elimination of the dye in the urine should be 60 per cent. in one hour instead of the two hours and ten minutes usually considered as normal after the intra-muscular injection. There is some danger, although it is so slight as to be almost negligible, that an irritation of the kidney may be produced in this way; hematuria has been

known to follow the intravenous use of phthalein. In certain conditions, notably pregnancy, destruction of the dye within the body seems to occur; at least it never reaches the kidney, and none at all or only small amounts are eliminated in the urine.

The normal excretion of phthalein is 60 per cent. or more in two hours (Rowntree and Fitz[4]), though in many instances the lower normal limit appears to be 50 per cent. In children the usual output is somewhat higher, 76 to 81 per cent. (Tileston and Comfort[5], Hill[6]).

Attempts to give the phthalein elimination a special significance as an index of either tubular or glomerular activity have not been entirely successful. With the study of the excretion of such substances as water, urea and salt, which are the natural products of metabolism and are continuously eliminated by the kidney, and whose excessive elimination or retention can now be more and more definitely interpreted in terms of renal disturbances, the phthalein test has been superseded. Studies of renal excretory products furnish a basis for deductions that lead to a more rational therapy and thus, in time, inevitably effect advances in clinical medicine, which a test with a more or less mechanical interpretation cannot do. The phthalein test is of particular value to the physician who has not specialized in diseases of the urinary tract and who wants to know in numerical terms to what degree the kidney is functioning satisfactorily.

Further Tests for Investigating Renal Function

The phthalein test has been described first because of its usefulness and its availability to every physician. There remain a very large number of more or less intricate procedures

for determining the activity of the kidney. It is difficult to select among these tests those that deserve to be used in more or less routine fashion for clinical purposes. It would seem to the author, after some years of study of this matter, that no particular tests really deserve preference. One of the chief factors is the skill and experience which a physician may have acquired with a given procedure. To a certain point the interpretation of any of the kidney function tests may be made according to a table or set figures, but a full realization of the significance of these tests will come only to the physician, who has carried out very many of these observations and has become so familiar with them that he understands their many variations. Tests for renal function may be divided into two groups: one of these is of recent development and we owe to the vision of Addis and Van Slyke and their co-workers methods by which the total amount of functioning tissue in the kidneys may be determined; the other group of tests aims at determining whether the kidneys under customary conditions of diet, activity, etc., are capable of maintaining the blood and tissues free from the accumulation of urinary excretory products. These two groups of tests for kidney function at first glance may be considered as duplicating one another; however, this is not the case, as will be shown below.

The amount of functioning renal tissue may be determined according to Addis[7] *or by the "blood urea clearance" of Austin, Stillman and Van Slyke*[8], later elaborated by Möller, McIntosh and Van Slyke[9]. According to Mackay and Mackay[10], and subsequently verified by Möller, McIntosh and Van Slyke[11], the loss of functioning renal tissue exceeds 50 per cent. before the usual tests for renal function, that is, the blood chemistry, the dye and specific gravity tests, give any indication of im-

paired activity. This, at first sight, would seem to be a grave fault in the methods we have been accustomed to regard as satisfactory for testing renal function. However, from a different angle, this fact has been appreciated for a long time. It is well known that when half of the kidney tissue is removed, as in unilateral nephrectomy the remaining kidney assumes the duty of both without any apparent insufficiency. Foster[12] has shown this to be true.

While we know that the usual tests for kidney function furnish an intimation of impaired kidney activity only when 50 per cent. or mo e of the renal tissue is destroyed, it must be borne in mind that the remaining 50 per cent. is adequate to maintain life and to perform all the functions ordinarily required of the kidneys. The question asked in the usual tests for renal function is how efficiently the available kidney parenchyma is eliminating the renal excretory products, and this the customary tests tell us very clearly. On the other hand, when it is desired to know how much damage has been done to the kidney, so that its approximate margin of safety may be determined, the procedures, which reveal how much kidney tissue remains, may be very useful. In considering these matters, it should not be forgotten that the type of pathological process is the greatest determining factor in the rapidity and the extent of the destruction of kidney tissue. Thus, it is necessary to know whether a patient is suffering from acute nephritis, arteriosclerotic nephritis, focal nephritis, or chronic diffuse nephritis. Not only the type of nephritis but likewise its etiology will have a bearing in this connection. It is, therefore, evident that the pathology of the kidney must be carefully considered in estimating kidney function and in making a prognosis.

The blood urea clearance test of Austin, Stillman and Van Slyke[8] estimates the amount of actively functioning kidney tissue. In this respect it is unique, and it promises to be one of the most important tests for renal function at our command. It fills a very distinct need for two reasons:

1. Since it is now recognized (Mackay and Mackay[10] and Möller, McIntosh and Van Slyke[11]) that the usual tests for kidney function may indicate impairment only when 50 to 60 per cent. of the renal tissue has been put out of commission, a procedure, which detects functional impairment when the first half or less of the kidney substance is rendered inactive, has obvious advantages.

2. The urea clearance test is probably the most accurate means to determine the percentage amount of functioning kidney tissue; not only is information furnished of the immediate state of affairs, but by successive tests, at longer intervals, a fairly accurate impression may be gained also of the progress of kidney destruction that is taking place in the patient with Bright's disease. Thus, we have here a means, more satisfactory than any heretofore, of measuring the rate of progress of nephritic lesions.

The determination of the blood urea clearance is described by Möller, McIntosh and Van Slyke[9] as follows:

Calculation of Clearance Values

"If the urine volume exceeds 2 c.c. per minute, as observed in an adult, or as corrected for body size in a child, the *maximum clearance* is calculated.

"If the volume thus observed or corrected is less than 2 c.c. per minute, the *standard clearance* is calculated.

"It is advantageous as a rule to calculate both clearances in percentages of the mean normal C_s and C_m. Urea excretions observed with

ordinary urine volumes and calculated in terms of C_s are thus rendered directly comparable with excretions observed with large urine volumes and hence calculated in terms of C_m. Furthermore the percentage values thus calculated express directly percentages of average normal renal efficiency.

"The percentage of average normal C_m is obtained by dividing the absolute C_m value by the mean normal C_m, 75, and multiplying by 100. Similarly the percentage of average normal C_s is obtained by dividing the absolute C_s by 54 and multiplying by 100.

$$\text{Per cent. of average normal } C_m = \frac{100\,UV}{75B} = 1.33\,\frac{UV}{B}$$

$$\text{Per cent. of average norma } C_s = \frac{100\,U\sqrt{V}}{54B} = 1.85\,\frac{U\sqrt{V}}{B}$$

"*Graphic calculation of C_m and C_s.* Both the absolute and percentage C_m and C_s values are most readily calculated graphically by means of a slide rule, or by means of the line charts. (NOTE: The line charts may be found in the original article but are not reproduced here).

"*Arithmetical calculation of C_m and C_s.* For arithmetical calculation of the standard clearance the following values of the square root of V are given covering the range below the augmentation limit.

V *c.c. per minute*	$\sqrt{V}$	V *c.c. per minute*	$\sqrt{V}$
0.2	0.45	1.2	1.10
0.3	0.55	1.3	1.14
0.4	0.63	1.4	1.18
0.5	0.71	1.5	1.23
0.6	0.78	1.6	1.27
0.7	0.84	1.7	1.30
0.8	0.89	1.8	1.34
0.9	0.95	1.9	1.38
1.0	1.00	2.0	1.42
1.1	1.05	2.1	1.45

Example of calculation of a normal maximum clearance

Blood urea N = 15.6 mgm. per 100 c.c. = B

Urine urea N = 321.0 mgm. per 100 c.c. = U
Urine volume = 210 c.c. per hour
= 3.5 c.c. per minute = V

$$C_m = \frac{UV}{B} = \frac{321 \times 3.5}{15.6} = 72 \text{ c.c. of blood cleared of urea per minute}$$

Per cent. of average normal function = $1.33 \times 72 = 96$ per cent.

Example of calculation of a normal standard clearance

Blood urea N = 14.7 mgm. per 100 c.c. = B
Urine urea N = 750 mgm. per 100 c.c. = U
Urine volume = 50 c.c. per hour
= 0.83 c.c. per minute = V

$$C_s = \frac{U\sqrt{V}}{B} = \frac{750 \times 0.91}{14.7} = 46 \text{ c.c. of blood cleared of urea per minute}$$

Per cent. of average normal function = $1.85 \times 46 = 85$ per cent.

"*Technique for determining the blood urea clearance as a measure of renal efficiency.* The necessary data are the concentrations of urea in blood and urine, and the volume of urine excreted in a measured time. The manner in which these 3 values are secured may be varied to suit conditions. As a routine procedure, however, we have found the following satisfactory:

The subject is not subjected to any previous routine, except that vigorous exercise is avoided and the previous meal should be a moderate one, preferably without coffee, which Addis and Drury (1923) have found may increase the blood urea clearance. The most desirable time of day, when excretion is least liable to fluctuations, is found according to MacKay (1928) in the hours between breakfast and lunch. The patient remains quiet while the urine is collected during two succeeding periods of 1 hour each. The chief source of error is probably the possibility of incomplete emptying of the bladder, either at the beginning or end of a period. The collection of two urine specimens affords a check on this factor. A few minutes before the end of the first hour a blood sample is drawn. Its urea content is used for calculation of the clearances during both periods. This usage is permissible, because under the conditions of the test the blood urea does not change greatly during an hour.

"The maximum clearance is calculated if the urine volume observed in an adult, or if the corrected volume $V \times \frac{1.73}{\text{Sq. m. surface area}}$ in a child, exceeds 2 c.c. per minute.

"The standard clearance is calculated if the urine volume, corrected n the case of a child, is less than 2 c.c. per minute.

"*Physiological and pathological significance of maximum and standard lood urea clearances.* The excretion rate observed with the average nor- nal maximum blood urea clearance is what would be obtained if 75 c.c. f blood per minute passed the kidneys, and all its urea were excreted. Actually a larger volume of blood perfuses the kidneys, and only a cer- ain fraction of its urea is removed. Picard (1856) found that in dogs he urea content of blood from the renal vein was half that of blood from he artery. If a similar relation held for man, the average normal renal lood flow could be estimated at 150 c.c. per minute, 50 per cent. of the rea of this blood being excreted with large urine volumes and 35 per ent. with the average urine volume of 1 c.c. per minute.

"*Decrease in the volume of blood cleared of urea per minute in patho- ogical conditions must be due to one of two causes: either the volume of blood er minute passing through the kidneys is diminished, or the proportion of ts urea removed during the passage is less than normal.* In cardiac decom- ensation presumably the flow factor is responsible for lowered renal unction; and in glomerular nephritis the damaged renal vessels make liminished flow again seem certain. Whether a decrease in the propor- ion of urea removed from the blood also occurs or not, we have not at resent the basis to surmise."

The per cent. of average normal function, determined by his procedure, varies somewhat in persons whose kidney ctivity is normal or nearly so (80 to 110 per cent. are not nusual variations, and occasionally the percentage may be even lower or higher). The results assume a constancy directly roportional to the degree of impairment of renal function (that is, in chronic renal disorders, naturally not in acute disturbances of function, e.g., passive congestion, acute inflam- nation of the kidneys, etc.). This is probably due to the fact that in normal individuals, or those with a large factor of safety, the various forces contributing to the production of urine (number of active glomeruli, blood pressure within the glomeru- ar capillaries, etc.) are not acting constantly at maximal capac- ty, whereas in the subject whose kidney function is impaired

all forces influencing the output of urine are called into play and are working without respite at something approaching utmost effectiveness. The same facts are expressed in such patients by the fixation of the specific gravity and the constant, steady polyuria. Uremia, due to retention of urinary excretory products, is considered imminent only when the urea clearance shows that about 10 per cent. of the original kidney tissue is active.

For the reasons given above, we believe that the *tests which determine the ability of the kidney to prevent the accumulation of urinary excretory products within the body* give an answer to the question of how well the remaining renal tissue can cope with the dietary and metabolic burden imposed upon it and in that way furnish a satisfactory answer to the problem that concerns us in clinical medicine. Therefore, it is desired, for the time being at least, to confine the present practical discussion to such procedures.

There are many tests of this kind. It is impossible to describe all of them. It should be the aim of any practicing physician to become thoroughly familar with a few and not to attempt too many. The tests chosen here are perhaps those simplest to carry out and are those that the author has been using for a considerable length of time and feels that he can present more adequately than he could some others, although he realizes that these may be equally efficient and practical.

The *blood chemistry*, as it has been made available through the micro-methods of Folin, Benedict and Van Slyke, has contributed a great deal to the better understanding of Bright's disease; especially has the fact that albuminuria, increased arterial pressure and certain forms of uremia often occur without an accumulation of urinary excretory products within the body, made it clear that "nephritis" is a collective term for

a variety of constitutional disorders and is not solely nor even predominantly characterized by diminished kidney function. Which of the substances in the blood it is desirable to single out for study as the most significant (obviously there are too many to use them all) is a difficult task. By consensus of opinion they are, in the order of their clinical importance, urea nitrogen, creatinine and uric acid. This list, it is true, includes only the non-protein nitrogenous constituents of the blood and does not stress phosphate, calcium, CO_2 combining power, cholesterol, albumin and globulin; all of these are known to have a definite clinical bearing but have proved to be of more worth in the study of some especial features of uremia, edema and nephrosis than in determining renal function in the usual case of Bright's disease.

A survey of the amounts of the various non-protein nitrogenous constituents of the blood and of muscle are given in table 35. It is readily noted that the *amino acid nitrogen* does

	Normal Average Values for this Series		Retention Uremia Marked Renal Insufficiency Maximal and Minimal Values	
	Blood	Muscle	Blood	Muscle
N. P. N.	28.6	166	138–426	301–657
Urea N.	12.2	13	89–351	123–258
Uric acid	1.8		2.7–8.7	
Creatine	4.2	350	9.2–48.8	287–466
Creatinine	1.3	5	7.7–21.3	10–25
Amino Acid N.	7.9	32	4.9–11.8	22–39

TABLE 35. — The non-protein nitrogenous constituents of the blood and muscle, mg. per 100 c.c., in a series of normal persons and patients with marked renal insufficiency. (The normal human muscle was obtained from tissue removed at operations for carcinoma of the breast).

not increase in the blood no matter how deficient the kidneys may become. A rise of the amino acid nitrogen is associated

usually with an extensive destruction of liver tissue and is not related to renal disorders. The *creatine* in the blood becomes elevated so late in the course of Bright's disease that it may be looked upon as a terminal event, and the determination of this substance has no place among routine measures of renal function.

The *total non-protein nitrogen* (N.P.N.) method is resorted to widely as a test for kidney sufficiency. It is very valuable in this respect; however, it is doubtful whether it equals the estimation of urea. The methods for the determination of N.P.N. are not standardized as well as those for urea and yield divergent results; the quantitative analysis of N.P.N. demands finer chemical technique than that for urea, and consequently the average laboratory is more likely to err with the former than with the latter; as kidney function becomes deficient, the urea rises in the blood more rapidly than the N.P.N. and consequently presents a more vivid index of the progress of events; the blood urea in diseases of the kidney and allied conditions has been investigated much more thoroughly than any other substance and thus furnishes a more satisfactory basis for clinical judgment.

By common consent, uric acid, creatinine and urea have been regarded the preferred test substances. This choice has rested largely on the researches of Victor Myers and his associates, who formulated the idea that, as renal insufficiency developed, there was successive retention of uric acid, urea and finally creatinine within the blood (Chace and Myers[13], Myers, Fine and Lough[14]). An approximate sequence of what may be expected in regard to these is given in table 36. A great many objections have been raised, and numerous exceptions found to this scheme of stepladder-like heaping up of uric acid, urea and

Impairment Renal Function	Normal	+	++	+++	++++
Uric Acid mg. per 100 c.c.....	3	3–5	6–8	9–10	11+
Urea N. mg. per 100 c.c.....	15	15	15–40	40–65	65+
Creatinine mg. per 100 c.c.....	2	2	2	2–5	5+

TABLE 36. — Blood chemistry, as a measure of renal function.

creatinine within the blood, but taking all the facts into consideration it still retains its usefulness. It is applicable only to the uncomplicated case of chronic Bright's disease; pathological changes in other organs (e.g., pneumonia), pathological-physiological processes (e.g., gout), or variation of normal functions (e.g., low protein, high carbohydrate diet) may interfere with the literal interpretation of these figures. However, this does not detract from the value of this plan but should serve only to render us very circumspect in drawing conclusions from the blood chemistry; possibly, in many instances, deviations from the expected may point the way to a better diagnosis and even to a discovery of new facts. In the following paragraphs this subject will be analyzed a little more closely.

The Uric Acid of the Blood. — While this may be the first substance to increase as the result of incipient renal insufficiency (tables 36, 45, 51), it may be normal even with advanced impairment of renal function (table 35). Furthermore, there are many conditions in which the blood uric acid rises above the normal apparently as the result of some "metabolic disorder" and not because of any diminution of kidney function (see table 37). This has come to our notice particularly in renal calculus and allergic disturbances such as asthma, urticaria, eczema, etc.; the high uric acid content of the blood in gout and leukemia is well known. Fishberg[15] finds that in essential

Diagnosis	Uric acid in the blood mg. per 100 c.c.	Urea N. in the blood mg. per 100 c.c.
Polycythæmia....	6.8	7.8
Renal Calculus...	7.5	15.3
Eczema.....	5.0	11.2
Keratitis.....	7.5	17.0
Catarrhal Jaundice	6.3	10.8
Asthma.....	5.8	14.0

TABLE 37. — Examples of a disproportionate elevation of uric acid in the blood not due to renal insufficiency. This is a common occurrence.

hypertension the rise of the blood uric acid alone, without an accompanying increment in the blood urea, is of no prognostic significance and does not require any dietetic or other treatment. This is perfectly true and is a precept that has been followed for a long time. However, to argue from these conclusions that a concentration of uric acid above the normal may not be indicative of a certain degree of renal insufficiency, at least, is going further than the facts warrant. The rate of progress of a renal insufficiency should be judged by the pathological lesion responsible for the condition and not directly by any estimate of renal function; the patients described in tables 45 and 51 were, at the time of the examination, subject to about the same degree of impaired kidney activity, a very slight one, indicated by the high blood uric acid values as virtually the only signal; yet the patient with hypertension has lived a long time and presumably will succumb to either apoplexy or cardiac failure, while the patient with chronic nephritis died of retention uremia, the result of kidney insufficiency, within two years. Though a "hyperuricemia" may be diagnostic of renal insufficiency, it is doubtful whether the information conveyed by the estimation of uric acid in the

ood is of sufficient importance to make it worth resorting to a routine procedure. This leaves only two substances, the eatinine and the urea nitrogen, for consideration in the stomary blood chemical tests in the clinical study of Bright's sease.

The creatinine estimations in the blood have been interpreted ariously from time to time. At present the rather surprising nclusion of Behre and Benedict[16] appears to be accepted: Our finding that creatinine does not exist in blood in detectble quantities need not, of course, raise any question as to the alue of the determination of the chromogenic substance for inical or other purposes." In the subsequent discussion the erm creatinine is used to signify this chromogenic subtance.

Creatinine rises in the blood only when renal function has ecome markedly impaired (see table 36). A value of creatinine bove 5.0 mg. per 100 c.c. of blood is regarded as a sign hat there is very little margin of safety in the amount of active idney tissue and, by and large, the dictum of Myers and ough[17] holds true that death from retention uremia will follow ithin a comparatively brief period. It is an error to judge f prognosis solely on the basis of the level of the blood creainine; the underlying pathology and its course must be conidered in this connection. It has been pointed out frequently hat in acute conditions (acute nephritis, bichlorid of mercury oisoning, marked protein destruction such as in pneumonia, tc.), in which the kidney function often may be restored to ormal, not only the estimation of creatinine but any of the ther tests for renal function possess only temporary significance. n chronic diseases of the kidney the prognosis depends more pon the rate of progress of the renal lesion than upon the

creatinine figure. Thus, in polycystic kidneys the disease advances very slowly, and it is the rule, rather than the exception, that these patients live more than two years after the creatinine of the blood has risen to a level of 5.0 mg. per 100 c.c. O'Hare[13] has cited a number of cases of Bright's disease where low renal function was compatible with a long life. On the other hand, it is not rare to find persons suffering with Bright's disease who, within a year or two after they have exhibited perfectly normal kidney function, die as the result of renal insufficiency. A high blood creatinine, as well as other signs of marked renal insufficiency, are intimations of lack of reserve in the excretory power of the kidney and mean that there is danger ahead, but the proximity of a fatal issue rests largely on the rapidity with which the particular pathological process in the kidney advances to a point where the retention of urinary excretory products will cause death.

An analysis of the blood for creatinine is not indicated unless a distinct impairment of kidney function is suspected, either because some of the other tests are positive or because some clinical signs, e.g., anæmia or uremic manifestations, point in this direction. Creatinine is increased in the blood only when the activity of the kidney is not slightly, but markedly, curtailed; the level of the blood creatinine is not influenced by diet, as is the urea. For these reasons, creatinine determinations should be resorted to not as a routine procedure for testing renal function but as a confirmatory test, when an advanced degree of diminished excretory power of the kidney is suspected.

The blood urea nitrogen has been, and still is, the substance most generally tested; its direct estimation, as well as its relation to the urea in the urine as Ambard's constant, McLean's

ndex, the blood urea clearance test of Austin, Stillman and Van Slyke and others, has proved to be very valuable.

The level of urea nitrogen in the blood of normal persons varies considerably; the amounts regarded as normal are usually given as 12 to 15 mg. per 100 c.c. (tables 35 and 36). I have seen urea nitrogen as low as 4.5 mg. in the morning, before breakfast, in an individual who had been on a high starch, low protein diet for the three preceding days; this is worth remembering as some physicians believe that any figures lower than 7 or 8 mg. are the result of faulty chemistry; the same person, in the morning, fasting after a few days of his customary diet, had a concentration of 12 mg. per 100 c.c. of blood. MacKay and MacKay[19] find that in normal subjects the blood urea nitrogen may be as high as 23 mg. Values of 20 and over, however, should not be accepted as strictly normal without further investigation. Habitual indulgence in a very high protein diet will raise the blood urea nitrogen to 20 or even a little higher though the kidney function is not impaired. Each blood urea nitrogen determination may be regarded as the balance between urea production (protein intake, destruction and assimilation) and urea elimination for that individual's life up to the time of venipuncture. It is extremely satisfying to know that the laborious nitrogen balance observations carried through periods of weeks and months a generation ago can now be accomplished with more precision in a few minutes by a simple chemical test. It is usually advocated that venipuncture be done in the fasting state, before breakfast. From the clinical viewpoint it is justifiable to obtain specimens after intake of food; possibly it may even be preferable, since the effect of the diet may be studied to better advantage, and that is one of the prime objects of blood chemical examinations.

The relation between the blood urea concentration and th amount of functioning renal tissue has been investigated b MacKay and MacKay[19]. They find, according to their averag values, that as long as 50 per cent. or more of the kidne tissue is functioning the urea nitrogen of the blood is usuall not above 18 mg. per 100 c.c.; that is, it is practically withi normal limits. The failure of the routine functional kidne tests (except the urea clearance test) to detect the inactivit of the first 50 per cent. of renal secretory elements has bee mentioned in previous paragraphs of this chapter. When 1 to 20 per cent. of the renal tissue remained, the average ure nitrogen concentration in the blood was 44, when less than 1 per cent. remained the average blood urea nitrogen was 8 mg. per 100 c.c. of blood. In table 36 are given the conclusion of Mosenthal and Lewis[20] as to the degree of impairment o kidney function to be deduced from the blood chemical dete minations. From their clinical observations, they believed tha 65 mg. urea nitrogen per 100 c.c. of blood indicated destructio of kidney tissue close to the maximal degree compatible wit life; this would correspond to a 90 per cent. reduction o kidney substance, according to present interpretation. Recog nition of the fact that a urea nitrogen value in the blood of 6 to 80 mg. is a signal that only a very small margin of safet remains in the kidney, is extremely important for the clinicia to bear in mind. It is true that the urea nitrogen is usually a a level of 100, 200, 300, or even higher, when death fro retention uremia, that is, from renal insufficiency, occurs, bu it usually will hold true that, after the blood urea nitrogen ha reached a level of 60 to 80 mg. per 100 c.c., the final rise prone to occur with great rapidity, as the last bit of renal tissu that maintains life becomes destroyed.

It is generally recognized that the level of the blood urea depends largely on the diet. It has been mentioned how normal individuals, on a low protein diet, may show less than 5 mg. of urea nitrogen per 100 c.c. of blood, whereas those partaking of considerable quantities of protein may have 20 mg. or more. In Bright's disease with renal insufficiency the same fact holds true; thus in one instance it was possible with change of diet to reduce the urea nitrogen from 125 to 23 mg. One point here is worthy of note, and that is that even with the strictest dietary regulation in this very ill patient the blood urea nitrogen could not be brought to an absolutely normal level; this occurs frequently. The fact that urea in the blood fluctuates according to the diet makes this test for kidney function of peculiar value, inasmuch as it furnishes a guide to the quantity of urinary excretory products that are retained and thus measures the effectiveness of dietetic therapy.

It is now known that urea, in the amounts occurring in the blood and tissues even in very advanced stages of Bright's disease, is not a toxic substance. That our views in regard to this matter have changed a great deal is apparent from the older nomenclature, still retained, designating the terminal condition in Bright's disease as uremia. If the accumulation of urea is not the cause of death, why do physicians attribute so much importance to its level in the blood? The reason is simple: the fatal poisons, whatever they may be, parallel the retention of urea. Death from so-called uremia may occur from other causes than renal insufficiency, and hence all danger has not been set aside when the level of the blood urea has been reduced to what may be considered an innocuous point, that is, about 40 mg. of urea nitrogen per 100 c.c. of blood or less. If the blood urea is low, retention uremia will not occur, but

other forms of uremia (see chapter on uremia) may develop.

Another point that deserves attention is the fact that every increase in the blood urea is not necessarily the result of Bright's disease. Other kidney lesions, such as congenital polycystic disease or passive congestion, often are the cause. In cardiac failure the urea nitrogen often rises as high as 50 mg. per 100 c.c. of blood and sometimes higher; I have seen two cases, one where the blood urea nitrogen reached a level of 78, the other 150, which, at autopsy, showed passive congestion as the only renal lesion. Partial occlusion of the urethra through stricture or carcinoma, hypertrophy of the prostate gland, paralysis of the bladder in tabes dorsalis, spinal cord tumor and other involvement of the nervous mechanism of the urinary apparatus, double occlusion of the ureters from various causes and many other conditions lead to embarrassing mistakes in diagnosis. There are certain conditions in which there is a distinct increase in protein destruction and consequent rise in the blood urea. This has been demonstrated in infectious diseases, notably pneumonia, in peritonitis, in intestinal obstruction whether the occlusion is near the pylorus or at a lower level[21], at certain times in the course of Bright's disease and in other conditions. In its last analysis such a heaping up of blood urea cannot be regarded as the result merely of an increased destruction of protein, but must be due to a renal insufficiency as well, indicating a relative, if not an actual, diminution of excretory power; the kidney in the treatment of such a syndrome therefore deserves due consideration.

Alkalosis is accompanied by an increase in the non-protein nitrogenous substances in the blood and sometimes (see table 38) leads to needless worry; on the other hand, a severe

Date	Blood — mg. per 100 c.c.			CO_2 combining power blood. Vol. per cent.
	Uric acid	Urea N.	Creatinine	
Jan. 17	4.8	20.5	1.0	63
Jan. 29	6.0	41.5	3.0	77
Feb. 9	8.0	62.5	4.3	81
Feb. 15	7.5	32.5	3.0	76
Feb. 23	3.8	19.0	1.0	59

TABLE 38. — Male, age 22. Convalescing from an attack of acute Bright's disease. Rise in blood uric acid, urea N. and creatinine accompanying an alkalosis induced by the administration of bicarbonate of soda; the blood chemistry returned to normal when the medication was discontinued, and the alkalosis was set aside.

alkalosis frequently terminates fatally, and the retention of urinary excretory products is without doubt in part responsible for the serious aspect of the condition. Temporary or partial intestinal obstruction, especially in elderly or asthenic individuals, after operations or complicating gastro-intestinal disturbances, often is accompanied by varying degrees of renal insufficiency, where kidney function previously has been very satisfactory, and may modify the course of events in a very serious and unexpected fashion.

In acute conditions, acute nephritis, acute nephrosis as induced by bichlorid of mercury, etc., the retention of nitrogenous bodies in the blood has not the same significance as in chronic forms of kidney involvement. The renal insufficiency must be judged largely according to whether the underlying pathology will clear up, remain stationary or progress. The accumulation of blood urea nitrogen in acute nephritis, severe passive congestion, bichlorid of mercury poisoning or pneumonia will diminish as the disease responsible for it is ameliorated or cured. A renal insufficiency of a week or two weeks does no lasting harm, if the process then is relieved. A

fatal issue in acute Bright's disease, cardiac failure, or pneumonia usually is not brought about by retention of products ordinarily eliminated by the kidney but is induced in other ways. Similarly, the prognostic significance of blood urea nitrogen in chronic kidney disease must be interpreted according to the type of renal lesion responsible for its retention. What has been said in regard to the prognostic value of the blood creatinine, applies likewise to the urea nitrogen and need not be repeated here.

Urea Content of the Saliva. — Recently attempts have been made to resort to the determination of urea in the saliva at times when the estimation in the blood was impracticable. Schmitz[22] found that the urea content of the saliva averaged 89.4 per cent. of that of the blood. Hench and Aldrich[23] showed that the combined urea and ammonia nitrogen of the saliva rises roughly in proportion to the increase of the blood urea nitrogen due to renal insufficiency. Later these authors[24] formulated a "salivary urea index" by which renal function could be estimated. Stealy[25] finds that this index is satisfactory in normal persons, but that when renal insufficiency exists, there is a wide variation between the expected urea nitrogen as indicated by the salivary urea index and the actual blood urea nitrogen.

The Specific Gravity Determination of a Single Specimen of Urine. — This determination in a specimen voided at any time of the day or night, is the most readily available and, by far, the simplest of all the tests for renal function. It has been neglected very largely, because its plainness has lacked imaginative appeal, and because urinary specific gravity readings are carried out rather carelessly in many laboratories.

The formula for the interpretation of the specific gravity

of a single casual specimen of urine is as follows. The kidney function is normal, if the specific gravity is 1.020 or higher, unless there is a retention of water and salt, that is, passive congestion of the kidney or acute or chronic or nephrotic Bright's disease accompanied by edema. In other words, a urinary specific gravity of 1.020 or higher in any specimen of urine indicates that the kidney function is adequate to excretion of solids, and that if any impairment exists, it is due to the retention of water. This is a broad statement, but in our experience, thus far, there have been very few exceptions to it, and it has proved to be very helpful. The occasional exceptions observed have been in the cases of alkalosis and also in intestinal obstruction and peritonitis alluded to above. In these conditions the specific gravity of the urine may be 1.020 or more, and, at the same time, there may be a marked accumulation of urea in the blood. To think of the kidney function in these cases as normal and the increase in the blood urea as due to protein destruction, does not clarify the clinical diagnosis, nor would it be of any practical value to distinguish between relative and absolute renal insufficiency. These complications, excessive administration of alkalies, repeated vomiting, intestinal obstruction (however slight) and peritonitis must be kept in mind always as possible causes for diminution of kidney function, even though the specific gravity of the urine is 1.020 or higher.

Any high specific gravity reading is really equivalent to a concentration test, and such a formal procedure is unnecessary, if, at any time the urine is found to have a specific gravity of 1.020 or more. It must be understood that a specific gravity of 1.020 or higher, like all the recognized tests for renal function, except the urea clearance test, does not necessarily indicate that more than about 50 per cent. of the original kidney tissue

is active; however, it does mean that there is at least enough reserve power in the kidney to carry on without danger from renal insufficiency, except through possible fluid retention in the conditions mentioned above.

It is worth remembering that in passive congestion the specific gravity of the urine is fixed at a level of 1.018 to 1.025 (see table 46), while in acute Bright's disease, though it may be found at this height, it often rises to 1.040 or even 1.050. When, in edematous conditions, the fluid is no longer retained, that is, when edema is diminishing and polyuria comes on, the specific gravity is usually no longer elevated (for the possible changes that occur under these circumstances see tables 42, 43, 45).

The urine may, of course, be of low specific gravity in individuals whose kidney function is normal. However, it must be kept in mind that the only urinary sign of a maximal curtailment of renal activity may be a specific gravity of 1.010 or lower. It is a common experience to find urine specimens that are free from albumin and casts with a specific gravity of about 1.010 in patients whose blood urea nitrogen is 100 mg. per 100 c.c. This is notably true in cases of the advanced stage of primary contracted or arteriosclerotic kidneys. If such urines are passed on as satisfactory, and an operation is performed, or the patient undergoes any severe strain, uremia is likely to be precipitated. It is, therefore, an excellent rule that, when there is any reason whatsoever to suspect that renal function may be impaired, no patient's kidney activity should be assumed to be adequate to maintain life, without further investigation, unless the specific gravity of the urine be at a level of 1.020 or higher.

The dilution and concentration test, according to Pratt[26], was introduced as early as 1900 by Kövesi and Roth-Schulz; the

freezing point determination in their procedure was replaced by specific gravity readings by Hanssen, and the test subsequently was popularized by Volhard. Volhard[27] suggests that the test be carried out as follows:

Dilution test: The fasting patient empties the bladder and then drinks 1½ litres of water or weak tea; 30 to 45 minutes are allowed for the drinking of this fluid; the patient must be lying down and void urine every ½ hour; the volume and the specific gravity of each specimen are measured accurately (care must be taken that the specific gravity determinations are corrected according to the temperature of the urine). After four hours, when the ingested fluid will have been eliminated by the normal person, the *concentration test* is begun; the patient is now given a dry diet (no soups, no liquids); the urine is voided every hour or two; if by evening the specific gravity is not elevated, the test may be continued as long as 48 hours.

The amount of fluid required at the beginning of the test varies from 1,000 to 3,000 c.c. according to different investigators. One thousand c.c. of liquid taken within 5 to 10 minutes has proved satisfactory. In some clinics a dry breakfast is allowed immediately after the fluid, initiating the dilution test, has been taken, and the eating of solid food is not postponed until the concentrating power of the kidney is being investigated.

The criteria of what may be looked upon as normal differ in detail according to various authors, but in general are somewhat as follows: Within four hours after the taking of the fluid, approximately the total amount should be eliminated by the kidneys and the lowest specific gravity should be between 1.001 and 1.004; the urinary volume in this period may exceed the liquid taken; this occurs in healthy persons, or it may be

an early sign of kidney involvement (Schlayer was the first investigator to stress the fact that a slight lesion of the kidney may result in superfunction, and only severe impairment produce hypofunction; this was subsequently found to be true in measuring kidney activity by means of Ambard's constant or the phthalein test); during the concentration test the specific gravity should rise at least to 1.025 or 1.030 and may go higher. A normal result of the dilution and concentration test is given by Pratt[26]:

Time	Urine		Mrs. M.
	C.C.	Sp. Gr.	
8 A.M.	90	1.015	Intake 7 A.M., 1000 c.c.
9	370	1.003	Intake 8.35 P.M., 130 c.c.
11	570	1.003	Total intake, 1130 c.c.
1 P.M.	215	1.010	Total output, 1675 c.c.
3	110	1.014	Output in first four hours,
5	40	1.027	1030 c.c.
7	50	1.020	Maximum specific gravity, 1.027.
9–7 A.M.	140	1.024	Minimum specific gravity, 1.003.

TABLE 39. — Normal response of the concentration and dilution test as given by Pratt[25]. Note that within four hours after the taking of fluid practically the entire amount has been eliminated and the urinary specific gravity has been depressed below 1.005; subsequently during the dry diet period the specific gravity rises above 1.025.

The results in many normal individuals do not measure up to these standards either in the degree of dilution or concentration; this has been ascribed to the effects of excessively dry or excessively liquid diets on the days preceding the test. In a series of over 100 concentration experiments on normal persons, I found that about 10 per cent. failed to reach a specific gravity of 1.020 after 16 or 18 hours of a fluidless existence[30]. Pratt[26] notes the lack of the expected dilution in some of his normal control series. The conclusion may be reached that

moderate deviations from the normal standard in a dilution and concentration test need not necessarily indicate impairment of kidney function.

This procedure is contraindicated where the administration of a considerable amount of fluid imposes a severe strain, that is, in myocardial insufficiency, asthmatic states, any edematous condition whether associated with heart affections or Bright's disease, ascites from any cause, etc. As mentioned above, a study of the specific gravity of single specimens of urine in renal disorders usually serves to throw considerable light on the situation.

When kidney function becomes very markedly impaired, the variations of the urinary specific gravity diminish very much; even under the stress of forced dilution and concentration does this hold true. Patients, whose renal activities have undergone the maximal curtailment compatible with life, void

Normal Concentration			Moderate Impairment Concentration			Maximal Impairment Concentration		
Time	Urine c.c.	Urine Sp. G.	Time	Urine c.c.	Urine Sp. G.	Time	Urine c.c.	Urine Sp. G.
11.15	120	1.020	11.00	200	1.013	11.00	240	1.010
3.40	180	1.026	2.20	220	1.014	1.20	200	1.010
9.00	160	1.028	5.40	180	1.016	4.15	270	1.011
4.45	110	1.032	8.00	160	1.018	7.45	190	1.011
			12.00	120	1.018	10.20	310	1.012
			4.30	110	1.017	1.00	240	1.011
						4.40	180	1.012
	570			990			1630	

TABLE 40. — Concentration tests showing the normal, the result with moderate and maximal impairment of renal function; the kidney with no margin of safety cannot concentrate at a higher specific gravity than 1.012. The presence of a compensatory polyuria is beautifully shown in the cases with diminished renal activity (compiled from Rosenberg[28]).

urine with a specific gravity close to 1.010; under the influence of the dilution and concentration test their urine may show a variation of specific gravity from 1.005 to 1.012. Under the circumstances, the effects of forced fluid yield results which approximate the normal, and it is mainly the ability to concentrate that interests us. Such results are given in table 40. Care must be exercised in estimating these results since extra-renal factors, such as severe anæmia or the elimination of retained edematous fluid, may distort them; kidney conditions other than Bright's disease, e.g., urethral or bilateral ureteral obstruction, pyelitis, polycystic kidneys, paralysis of the bladder, etc., may of themselves yield similar specific gravity readings. The concentration test has been used widely because of its simplicity. Thus Fishberg[29] advocates a procedure by which the patient, having taken an early supper the evening before, voids three specimens of urine at about 8, 9 and 10 A.M. "If kidney function is unimpaired, the specific gravity of at least one of the specimens will exceed 1.024, often going as high as 1.032." In 1920 Mosenthal[30] published results of a similar test on about 100 normal persons and found that frequently the specific gravity was not as high as 1.020 and very often below 1.024. It would appear that this method, unless checked up by other tests for renal function, is not to be relied on for final results. Here we have the same limitations, which we found in the interpretation of the specific gravity of a single specimen of urine.

The Urea Concentration Test. — This test, conceived by MacLean and de Wesselow, utilizes the percentage of urea in the urine to determine the concentrating power of the kidney. This method of estimating renal function has been employed successfully by MacLean[31] as a routine clinical procedure and is extensively

used in England and elsewhere. An understanding of the factors influencing the concentration of urea in the urine is very helpful to all who are treating Bright's disease. MacLean[31] (page 58) described the mode of carrying out the test as follows:

"The patient is asked to empty the bladder, and immediately afterwards he receives by mouth 15 gm. urea dissolved in about 100 c.c. of water. The bladder is emptied one hour and two hours after the urea has been given, and the specimens of urine examined for urea content. Thus, if urea is given at 10 A.M., a specimen of urine is obtained at 11 A.M. and at 12 A.M. If either specimen gives a percentage of urea above 2, the kidneys are held to be fairly efficient; the higher the concentration the more effective is the renal function. The reason why two specimens are taken is that in certain patients the urea given by mouth may produce a diuresis which tends to dilute the urine passed during the first hour. In this case the second hour's specimen should be examined. Indeed, in routine work it is generally best to discard the first specimen altogether, and to rely on the result obtained from the second specimen. Not more than about 120 c.c. urine should be passed in the second hour. Occasionally, if there is much available fluid in the patient's system, it may be necessary to take a specimen after three hours, or even to repeat the test, but this is seldom necessary. In patients with marked diuresis this must be allowed for in estimating the renal function. In order to get accurate results and to avoid the tendency to diuresis, *it is essential that the patient should take as little fluid as possible for 18 to 24 hours before the test is carried out. This precaution probably enhances the average value of this test by at least 50 per cent., and the necessity for observing this direction cannot be too strongly emphasized. The stomach should also be empty, which means that the last meal taken by the patient should be a light one, and should be completed 3 hours or so before the test.*"

This test may be considered to indicate normal kidney function if the urea concentration is above 2.5 per cent. Marked impairment of renal activity exists if the percentage of urea is 1.0 per cent. or lower. In the terminal stages of progressive renal insufficiency, I have found a concentration of about 0.4 per cent. MacLean[31] describes a simple and ingenious apparatus for the determination of the urea by the hypobromite method.

The significance and the limitations of this test are about the same as those of the specific gravity measurement of urinary concentration. A percentage of 2.5 of urea in the urine indicates normal renal function except where the ability of the kidney to eliminate water and usually sodium chloride is limited; this occurs in passive congestion, in some forms of Bright's disease at times when edematous fluid is being accumulated, in all forms of intestinal obstruction whether partial or complete, in alkalosis and occasionally in other conditions. On the other hand, the urea concentration may be low and yet not indicative of impaired renal function, when the amount of urine is excessive as, for instance, when edematous accumulations are being eliminated in convalescence from cardiac decompensation, or from certain types of Bright's disease, also in the hyperfunctioning, polyuric stage accompanying all slight lesions of the urinary tract whether of the kidney, ureter, bladder or urethra, and in those instances where an excess of fluid has been taken on the previous days. Like all other tests for kidney function, the urea concentration test cannot be interpreted literally on a percentage basis only, but has to be considered in the light of many renal and extra-renal factors.

The Urea Tolerance Test. — This recently has been put forward by King[32]. This procedure is simple in execution and has proved to be of real value. It is carried out as follows: On the evening of the test, supper should be of low protein content and consist of fruit or vegetable salad; fluids should be restricted, and coffee and tea avoided; in the evening, at the beginning of the test, the patient voids, and the urine is discarded; subsequently all urine is collected for a period of 14 hours, that is, until the test is completed; an oxalated specimen of blood is collected at the beginning of the test; this furnishes the "con-

trol blood urea"; the patient is then given 1 gram of urea for each 10 pounds of body weight, i.e., 15 grams for an adult weighing 150 pounds; the following morning, fourteen hours after the ingestion of urea, another specimen of blood is taken and the urine is voided, thus completing the test; the patient remains in bed throughout.

The elevation of blood urea nitrogen above the rest level fourteen hours after the ingestion of urea is the basis of interpretation of this test; variations up to 2 mg. of blood urea nitrogen higher than the control figures are considered within normal limits, provided the output of urine is not excessive; under the conditions of this procedure with restricted fluid intake, a urine volume of over 750 c.c. for the fourteen-hour period is considered abnormal. By this test King found a retention of as much as 16 mg. of urea nitrogen per 100 c.c. of blood in fourteen hours.

The Two-hour Test for Renal Function. — This test was originated by Hedinger and Schlayer[33]. These authors devised a "nephritic test meal" containing reasonable quantities of fluids, salts and purins; the kidney activity was measured by the specific gravity and salt and water excretion in two-hourly periods. Mosenthal[34] subsequently measured the nitrogen (urea) excretion as well and found that not only could the degree of renal insufficiency be judged but, to a certain extent, its cause; later he showed that the type of diet within extremely wide limits did not interfere with the efficiency of the test; consequently *the procedure can be carried out on patients pursuing their usual occupation and diet. The results, under these circumstances, not only yield information concerning renal function but also show how the diet, the physical and the nervous efforts of the individual are adjusted to his or her hygienic needs and renal capacity.*

This method furnishes more satisfactory indications for treatment in office practice than can possibly be obtained by the very popular and often unnecessary "work up" in a hospital or under the artificial conditions imposed by many tests for renal function.

The various test diets that have been devised are not reproduced here, because they can be dispensed with and a great deal of fruitless labor is avoided if the food is not carefully weighed and measured. For some years we have been furnishing our patients with an ordinary traveling bag containing a wooden rack supporting eight, twenty-ounce, wide-mouthed bottles and have given them the following directions (it should be understood that *the hours given below are suggestions only; they should be changed as necessary to conform to the patient's daily habits*):

For: Date:

DIRECTIONS FOR "TWO-HOUR TEST"

Eat and drink what you are accustomed to. Note time and approximate amounts of food and fluid taken at each meal, on the back of this sheet, according to the following example:

8 A.M. Breakfast — 1 orange, 1 dish oatmeal, with cream and sugar, 1 slice buttered toast, 1 glass water, etc.

Any changes from the directions are to be noted on the back of this sheet.

8.00 A.M. Void urine and discard the urine.
8.00 A.M. Eat breakfast.
10.00 A.M. Void urine and place all in the labeled bottle.
12.00 Noon Void urine and save as before.
1.00 P.M. Eat lunch.
2.00 P.M. Void urine and save as before.
4.00 P.M. " " " " " "
7.00 P.M. " " " " " "
7.00 P.M. Eat supper.
10.00 P.M. Void urine and save as before.

All urine voided after 10.00 P.M. until 8.00 A.M. is to be placed in remaining one or two bottles and labeled 8.00 A.M.

8.00 A.M. Void urine and place in above bottle or bottles labeled 8.00 A.M.

Send the specimens to the laboratory by 9 A.M.

The means by which the two-hour test is evaluated are as follows:

1. *The specific gravity:* this determination furnishes about the same information as in the dilution and concentration test; it differs from the latter in that here no load is put upon the formation of urine, and the results not only measure renal function but also indicate the concentration of urine under habitual conditions and thus, through the physiological or pathological physiological facts developed, point the way to well defined dietary regulation and other therapeutic measures.

(*It should be understood that in examining the urines of the two-hour test, it is not obligatory to follow any one formula;* the urines may be tested for specific gravity only, or for volume, for albumin, glucose, salt, urea, or total nitrogen; or any of a number of investigations may be carried out according to the nature of the case and the desires of the physician.)

2. *The volume:* the same comments hold true as for specific gravity.

3. *Salt elimination:* this is a measure of the salt intake, unless salt is being retained as in passive congestion, some forms of Bright's disease, pneumonia, etc. The power of the kidney to concentrate salt may be judged.

4. *Nitrogen or urea elimination:* this is roughly proportionate to the protein intake. The concentrating ability of the kidney is revealed much as in the urea concentration test.

5. *Glucose:* this is of great help in distinguishing certain forms of glycosuria and discovering pentosuria, if the latter is kept in mind.

6. *Albumin:* the effect of rest and exercise and the diagnosis of an orthostatic type of albuminuria may be established.

The standards for the two-hour test are as follows:

Maximal specific gravity, normal standard: 1.020 or higher. This measures the ability of the kidney to concentrate the urine. Renal function may be inadequate even though the concentrating power is good. This occurs when water elimination is deficient and is often found in cardiac decompensation and in Bright's disease associated with edema; in complete or partial intestinal obstruction, at any level; as a sequel to severe vomiting or diarrhea from any cause; it has been noted in the oliguria following transfusions. The urinary specific gravity may be low though kidney function is excellent; in normal individuals the maximal specific gravity may be below 1.020 when a very large amount of fluid is being taken; in subjects that are eliminating retained fluid (edema, ascites, etc.); in severe anæmia; when the urinary tract is irritated as in cystitis, pyelitis, etc.; in diabetes insipidus. The lack of concentration in these instances is compensated for by an increased volume of urine. Ordinarily a low maximal specific gravity is believed to indicate diminished renal function. This is true as far as concentration is concerned; there may, however, be a compensatory polyuria, as in the conditions mentioned above, and frequently in chronic Bright's disease, that lifts the effectiveness of "renal function as a whole" to a degree adequate to the elimination of all excretory products at a normal rate. When the compensatory polyuria fails, retention begins, and the blood chemistry rises.

Variation of the specific gravity, normal standard: 9 points or more. Normal renal activity is characterized by a variation of 9 degrees or more in the urines of the two-hour test. A high

specific gravity with diminished variation may occur in normal persons because they take too little fluid to meet their bodily needs; on the other hand, when large amounts of fluid are being taken, the specific gravity may be more or less fixed at a low level. A high, fixed, specific gravity, at a level of 1.018 to 1.025, a low chloride and high urea concentration, characterize the urine of the passively congested kidney; in Bright's disease accompanied by edema formation the urinary specific gravity is also high and fixed, but the specific gravity may rise much higher than in the congested kidney, especially in acute nephritis, where it may attain a level of 1.045 or even 1.050. A low, very fixed, specific gravity, usually at a level of about 1.010, is found in chronic Bright's disease with a very marked impairment of renal function. Under extreme stimulation such kidneys can, at times, concentrate the urine to a specific gravity of 1.014 or dilute it to 1.005, but as a rule the variation from the highest to the lowest figure is about two points. It must be kept in mind that a low fixed specific gravity at a level of about 1.010 is found in many widely varying conditions; marked anæmia, elimination of edema, cystitis, pyelitis, polycystic kidney, prostatic hypertrophy, urethral stricture, paralysis of the bladder (as in tabes dorsalis or tumor of the cord) and others. A lower, fixed, specific gravity occurs in some diseases, notably diabetes insipidus.

Nocturnal polyuria, normal standard: 725 c.c. or less. If the collection of the night urine is begun about three hours after the evening meal and continued until the rising hour on the succeeding morning, and no fluid is taken after supper, the volume of urine in normal individuals is usually 400 c.c. or less, though it may be as high as 725 c.c. In cases with diminished renal function the amount is prone to increase so that it may be

necessary for the patient to void one to four or more times a night. Quantities as high as 1,200 c.c. frequently occur. The nocturnal polyuria is a process of elimination which compensates for a diminished excretion during the day. A study of the two-hour test may reveal the cause for the high night urine and thus afford the opportunity of doing away with it by suitable dietary regulation. Nocturnal polyuria often is a very early sign of impairment of renal function in Bright's disease; it is of great significance when present, but for some reason, not entirely clear, often it is absent. The lack of nocturnal polyuria does not necessarily point to the existence of normal kidney activity. In the present directions for the two-hour test, food and fluid are allowed after supper which, of course, precludes a strict interpretation of the quantity of the night urine but does furnish a picture of what takes place while the patient follows out his daily or nightly routine, and this has proved to be the more valuable from the clinical standpoint.

Sodium Chloride. — The quantity eliminated in the urine usually is equivalent to the intake. Eight to twelve grams of salt a day is the amount taken by the average person on a full diet; the so-called "salt-free diet" of the ambulant patient usually contains four to five grams, the hospital dietaries about three grams, though as Frederick M. Allen has shown, it is possible to reduce the sodium chloride to one-half gram a day, when the food intake is correctly supervised. At times patients who believe themselves to be indulging in proper diets eliminate as much as twenty or more grams a day. The power of the kidney to eliminate salt may be considered to be normal, if the concentration of the sodium chloride reaches one per cent. in any of the specimens of the two-hour test, but not necessarily abnormal, if it is lower, since the test is not designed to

elicit the sodium chloride concentrating power of the kidney. In passive renal congestion the salt elimination is very much diminished, and the urinary concentration of this substance is low and very fixed; in severe cases only mere traces of salt appear in the urine. In Bright's disease with edema formation salt is also retained; the low chloride elimination characteristic of pneumonia is well known.

Urea (total nitrogen). — Nitrogen × 2.14 = urea. Nitrogen × 6.25 = amount of protein represented by given quantity of nitrogen. The urea excretion is more or less directly proportional to the protein intake and in the two-hour test furnishes a rough estimation of the amount of protein food eaten. In clinical determinations the hypobromite method usually is resorted to for the estimation of urea. This gives satisfactory results which, however, yield values that are equivalent to all the nitrogenous substances in the urine and not to the urea alone (Mosenthal[30]). Consequently, the amount of urinary area divided by 2.14 and multiplied by 6.25 would yield the amount of protein represented by the urea. This would give a factor a little less than 3. Knowing that some of the nitrogen is eliminated by the intestinal canal, it is permissible to increase the factor, and it may be formulated that for approximate calculations *the amount of 24-hour urinary urea, as determined by the hypobromite method, multiplied by 3 is roughly equivalent to the protein intake.* The customary average protein intake is 60 to 75 grams. If the starches and fats are raised in the diet, the proteins can be lowered to about 30 grams without causing a deterioration of the tissues, as manifested clinically by secondary anæmia. In experimental work the protein foods can be reduced much further without resulting in a loss of nitrogen; however, this cannot be accomplished with the limited regulation that

can be accorded ambulant patients. The amount of urea eliminated must be regarded only as a very rough estimate of the protein intake, since it is never clear how much protein is being stored in the body, or how extensive protein tissue destruction may be. The retention of urea, which the kidney should eliminate, is judged best by the blood chemistry. A concentration of urea of two per cent. (nitrogen one per cent.) in any of the specimens of the two-hour test points to a normal concentrating power of the kidney for urea. In passive congestion or Bright's disease with edema, the concentration of urea remains high, though that of the salt is much diminished; a retention of urea under these circumstances is due to marked oliguria. In chronic Bright's disease, as renal function becomes impaired, the ability of the kidney to concentrate both salt and urea diminishes appreciably and in extreme instances reaches a point as low as 0.2 per cent. for the sodium chloride and 0.4 for the urea; in these cases the concentration of these substances varies very little in different specimens of urine, that is, the concentration becomes fixed.

The above discussion shows how many facts must necessarily be kept constantly in mind, if the specific gravity, the volume, the salt and the urea content of the urine are to be interpreted properly. This is not an easy matter, and the future promises further ramifications which will surely yield increased precision in diagnosing disease and faulty hygienic habits. This applies to all tests whether of dilution or concentration, whether measured by volume, specific gravity or urea or salt elimination. However, it is the author's belief that of all the methods of estimating renal function, the two-hour test, carried out while the subject is fulfilling his routine tasks and living on his customary diet, yields more data than any

other test now in vogue to enable the physician to interpret renal activity on a rational basis of physiologic efficiency or impairment. The urine analysis furnishes the picture of the excretory metabolism, if we may call it so; the blood chemistry, whenever available, is of the greatest value in supplementing the manner of elimination by revealing the condition of what may be termed the intermediary metabolism in the body.

Signs, Symptoms and Treatment of the Impairment of Renal Function Accompanying the Various Forms of Nephritis

Acute Diffuse Glomerular Nephritis

In many instances of acute diffuse glomerular nephritis there is no disturbance of renal function; these patients have blood and casts in their urine but no other signs or symptoms of Bright's disease, and, consequently, their condition frequently escapes diagnosis and treatment. Judging from the number of cases of chronic nephritis, which at their inception must have been acute in character, such a silent and insidious onset and course of an acute nephritis is of frequent occurrence.

When there is impairment of renal function, it is signalized by the retention of water and of salt; the power of the renal tissue to concentrate urea remains excellent in contrast to that for salt. If the oliguria becomes extreme, there may be a rise in the blood urea not due to an intrinsic inability of the kidney to eliminate urea, but because not enough water is excreted to carry away the urea. This type of diminished renal function is very similar to that found in passive congestion; it is largely the result of glomerular congestion either due to myocardial weakness or to an inflammatory process. On the other hand, in chronic glomerular nephritis, or any form of renal lesion such

as polycystic kidney or vascular nephritis, in which many of the glomeruli are completely or partially destroyed, while the remaining ones develop compensatory hypertrophy, the impairment of renal function comes about in another way: the ability of the kidney to concentrate urea and other solids in the urine is lowered; this is counterbalanced by an increased output of water so that an accumulation of renal excretory products in the blood is prevented through a compensatory polyuria; finally the fluid excretion also becomes diminished, and actual renal insufficiency is established.

The oliguria or anuria of acute diffuse glomerular nephritis depends on two sets of factors, the renal and the extra-renal. The renal cause is the inflammatory congestion of the glomeruli; the extra-renal factor is the retention of water and salt by the tissues, the result of a generalized capillaritis. The loss or increase of the patient's weight and all the signs and symptoms of edema (see chapter on edema), therefore, are an index of the state of kidney activity.

Dilution and concentration and two-hour tests often are impossible because of the small amount of urine voided, and the determination of the *specific gravity of the casual specimen of urine* is of the greatest importance in this disease. The points that should be kept in mind are the following:

1. *While oliguria exists, the specific gravity is 1.020 or higher*, rising as high as 1.050. In passive congestion the urinary specific gravity fluctuates between 1.018 and 1.025; in partial or complete intestinal obstruction and in the oliguria sometimes following transfusions of blood the specific gravity may be elevated also. The specific gravity is more or less fixed at a high level, while fluid is being retained (table 41); such a persistently raised specific gravity in acute diffuse glomerular

nephritis indicates good concentrating and impaired diluting power on the part of renal function.

Time	Volume c.c.	Sp. Gr.
8.00–10.00	60	1.030
10.00– 1.15	100	1.030
1.15– 5.30	100	1.030
5.30– 8.00	70	1.030
8.00–10.30	60	1.035
Total day	390	
10.30– 8.00	180	1.032
Total	570	

TABLE 41. — H. S., male, age 31. A fairly fixed specific gravity of the urine at a high level in a case of acute diffuse glomerular nephritis with marked oliguria and edema.

2. If the *specific gravity is low*, usually in the neighborhood of 1.010, *while oliguria is present during the first few days* of a disease that has been diagnosed as acute nephritis, then the diagnosis is incorrect, and there are two possibilities which call for urgent consideration: in the first place, such a specific gravity may be indicative of an acute exacerbation of a chronic glomerular or a vascular nephritis with marked impairment of renal function; in the second place, such a urine may not be that of an acute nephritis, but that of an obstruction of the urinary tract either in the ureters or urethra. On several occasions we have been fortunate enough to remove calculi, gravel or strictures of the urethra or ureters and remedy a precarious situation simply because reliable specific gravity determinations of single specimens of urine were available.

3. *A low urinary specific gravity in the third week, or later* of an acute nephritis, *while edema and oliguria remain marked*, should lead to investigations to determine whether the disease

has assumed the serious aspects of the subacute type of nephritis, which is discussed subsequently in this chapter.

4. *A low specific gravity of the urine usually indicates that polyuria has begun.* The transition from a limited to a copious urinary flow frequently is very abrupt, almost inconceivably so, as may be noted in table 42. Such a sudden change might be

Time of Day	c.c.	Sp. Gr.	Time of Day	c.c.	Sp. Gr.
8–10	102	1.017	8–10	40	1.021
10–12	90	1.020	10–12	63	1.021
12– 2	98	1.020	12– 2	35	1.020
2– 4	118	1.021	2– 4	57	1.018
4– 6	88	1.020	4– 6	83	1.017
6– 8	390	1.006	6– 8	228	1.009
Total, day	886		Total, day	506	
Night, 8–8	1280	1.010	Night, 8–8	1228	1.010
Total, 24 hrs.	2166		Total, 24 hrs.	1734	

TABLE 42. — Two examples of the sudden change that may take place in the urine output and specific gravity in acute diffuse glomerular nephritis when the patients begin to eliminate the retained edematous fluid; the sharp change from oliguria with a high specific gravity to polyuria and a low specific gravity is striking; this is apparently the exact time at which the kidneys began to eliminate the edema. Such a sudden change might be ascribed to a rapid clearing of the residual inflammatory products from the glomerular capillaries and a corresponding improvement in the circulatory flow within the glomeruli.

ascribed to a rapid clearing of the residual inflammatory products from the glomerular capillaries and a corresponding improvement in the circulatory flow within the glomeruli. When a polyuria and a low specific gravity have once begun they often continue for a long time, that is, until the edema has been set aside. Such a polyuria and moderate fixation of specific gravity are shown in table 43.

5. *The urinary specific gravity is not always lowered when edema is eliminated.* This holds true when the volume of urine, though not sufficiently large in amount to constitute a polyuria, yet surpasses the fluid intake; this might be regarded as a

Time of Day	c.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent.	Grams	Per Cent.	Grams
8–10	355	1.010	0.66	2.34	0.20	0.71
10–12	195	1.014	0.90	1.76	0.34	0.66
12– 2	290	1.011	0.64	1.86	0.28	0.81
2– 4	225	1.014	0.77	1.73	0.35	0.79
4– 6	180	1.014	0.89	1.60	0.37	0.67
6– 8	275	1.010	0.58	1.60	0.31	0.85
Total, day	1520			10.89		4.48
Night, 8–8	1660	1.010	0.60	9.96	0.21	3.49
Total, 24 hrs.	3180			20.85		7.97
Intake	680			8.50		3.89
Balance	– 2500			– 12.35		– 4.08

TABLE 43. — Characteristic urine of a case of acute Bright's disease while eliminating edema; polyuria is distinct; the specific gravity is moderately fixed at a low level in contrast to the period while fluid was being retained when the 24-hour volume was about 500 to 600 c.c. and the specific gravity fixed at a level of 1.020; note the large negative sodium chloride balance.

relative polyuria, and it indicates a gradual, rather than a rapid, subsidence of the glomerular congestion. Such a case is given in table 45 under chronic diffuse glomerular nephritis. The practical clinical point is that the specific gravity of the urine may be higher than 1.010 or 1.014, while the patient with Bright's disease is ridding himself of edematous fluid through the kidneys, and that this process must, at times, be judged by loss of weight and diminution of the subcutaneous swelling and not solely by the urine volume or specific gravity.

The *blood chemistry* may rise in acute diffuse glomerular nephritis. However, the significance of the accumulation of urea or other urinary excretory products is very different from that in chronic Bright's disease. In the acute condition the renal insufficiency, however severe it may be, is temporary and almost always rectifies itself in the course of a comparatively

brief period. Hence, when it does exist, it is not a cause for anxiety except for the rare occurrence of subacute diffuse glomerular nephritis.

The blood urea nitrogen usually is at a normal level; this is true whether symptoms of convulsive or sthenic uremia exist or not. It was one of the greatest surprises in the history of clinical medicine to find that the type of uremia characteristic of acute Bright's disease was not accompanied by an increase in the blood urea. It has been explained how the elimination of urea is normal, provided there is a sufficient amount of water secreted to carry it away; *when the oliguria is extreme, or when there is anuria, the urea is retained.* When the urinary flow is re-established the urea, which has accumulated in the blood, returns to normal. This course of events may be noted in table 44.

Date	Milligrams per 100 c.c. blood	
	Total Non-protein Nitrogen	Urea N.
October 27	60	45
November 1	57	36
November 3	49	27
November 30	32	22
December 6	19	12
December 8	14	9
December 13	16	9
December 20	18	8

TABLE 44. — Data from a case of acute diffuse glomerular nephritis demonstrating that the total non-protein nitrogen and urea nitrogen may be elevated in this condition and that they return to normal when the kidney lesion heals.

There may be extra-renal causes for a heaping up of urea in the blood; alkalosis (see table 38) and, at times, the acute infection responsible for the nephritis are associated with

increased protein destruction which results in the accumulation of the non-protein nitrogenous substances in the blood; it is appreciated generally that this often occurs in pneumonia even though no nephritis is present.

The treatment of impaired renal function in acute diffuse glomerular nephritis is covered in the section on the treatment of the renal lesions and that on the treatment of edema in acute diffuse glomerular nephritis. Since the occurrence of diminished renal activity usually is transient, and since it depends on the above two factors, its therapy is necessarily one that is directed towards allaying the inflammatory lesions in the kidney and in setting aside the retention of salt and water, that is, the causes which are active in the production of edema. Thus the handling of impaired renal function in acute diffuse glomerular nephritis rarely requires individual measures that are not already included in the urgent treatment which must be accorded this form of Bright's disease.

Subacute Diffuse Glomerular Nephritis

This form of Bright's disease is the rare sequel of the acute type of glomerular inflammation; it is invariably progressive and has a fatal termination within a few weeks to six months of the onset of the original acute diffuse glomerular nephritis. The diagnosis of this disease rests entirely upon the changes which take place in renal function. If in what appears to be a prolonged course of acute glomerular nephritis, signalized at times by a persistent edema and always by an albuminuria, the specific gravity is continuously at a level of 1.010 and the blood urea is distinctly elevated, the diagnosis of a subacute diffuse glomerular nephritis (fulminating type of acute Bright's disease) with a probable fatal outcome may be made confidently.

A case of this sort, confirmed by autopsy, is the following: Elizabeth K., age 8 years; slight blood stains were found on the child's bloomers 7 weeks before admission to the hospital; a day or two later the urine was frankly blood tinged; shortly afterwards the feet, abdomen, lumbar region and face became swollen; the family physician ordered the child to bed and prescribed a salt- and meat-free diet; the swelling disappeared. Evidently there had been an attack of acute diffuse glomerular nephritis, which was subsiding as shown by the diminution in the subcutaneous edema. One week ago fever and cough developed, and when the patient entered the hospital ward (October 29th), she had a frank left upper lobe pneumonia which was completely resolved 13 days later (November 11th). Following this there was a gradual accumulation of edema, which advanced progressively, deepening into marked anasarca; the extent of this may be judged from the fact that the body weight increased from 52 pounds on November 11th to 72½ pounds on December 13th; on December 19th uremic symptoms began, and the patient died on December 26th, 15 weeks after the hematuria was first noted. The diagnosis was made practically on one point, namely, the persistent low urinary specific gravity found in casual specimens of urine:

Date	*Urine — Sp. Gr.*
Dec. 2	1.012
5	1.010
6	1.012
7	1.010
8	1.010
9	1.012
10	1.010
11	1.010
15	1.010
16	1.012
18	1.010

The constant low specific gravity, while there was marked anasarca and oliguria, point to the destruction, probably through fibrosis, of many glomeruli; all the forms of Bright's disease associated with edema and oliguria (acute or chronic diffuse glomerular nephritis, edematous tubular nephritis, cardiac failure) except subacute diffuse glomerular nephritis would show a urine with a specific gravity of 1.020 or higher. The fact that the low specific gravity of the urine in this case is indicative of renal insufficiency is checked by numerous blood urea nitrogen determinations which varied from 56 to 240 mg. per 100 c.c. from October 11 to December 24th.

The treatment of the diminished renal function in subacute diffuse glomerular nephritis resolves itself into the therapy accorded retention uremia; the condition usually is hopeless, and what little chance there is of maintaining life consists in preventing the accumulation of urinary excretory products within the blood by a low protein and high carbohydrate diet and by meeting symptomatic indications as they arise.

Chronic Diffuse Glomerular Nephritis

There are three extra-renal influences that have a bearing on the way in which the kidney functions in chronic diffuse glomerular nephritis. These are edema, passive congestion resulting from cardiac weakness, and finally anæmia. None, or all, of these factors may influence renal activity in a case of chronic diffuse glomerular nephritis. It is necessary to have the characteristic effects of each one of these disturbances in mind when any of the tests for renal function in this disease is interpreted. It becomes evident that when *four major elements, edema, cardiac power, anæmia and kidney pathology* are involved in changing the kidney activity from the normal, that the

accurate interpretation of tests for renal function may be somewhat difficult and, at times, even impossible. However, the utmost we can do is to bear in mind the changes which these various elements produce, and analyze the results to the best of our ability, always correlating them with the clinical findings in order to clarify the situation as much as possible.

Edema, that is the retention of salt and water, may be present. This is accompanied by the same signs and symptoms, as far as the urinary specific gravity and increase in blood chemistry are concerned, as the oliguria in acute diffuse glomerular nephritis, and reference is made to the preceding section concerning these matters. Acute exacerbations of chronic diffuse glomerular nephritis are of frequent occurrence and naturally present the same picture as the acute attacks plus the background of whatever chronic process may have preceded it

The changes in the urinary specific gravity and volume of urine in chronic nephritis usually are less abrupt than in the acute form. This may be noted in table 45, which portrays a stage in which the patient is eliminating the fluid derived from edematous accumulations and doing it without a spectacular polyuria or a very low urinary specific gravity.

As a rule, the natural course of events in cases of chronic diffuse glomerular nephritis is a progressive inability to concentrate the solids in the urine, especially the urea and sodium chloride. The retained urea evidently acts as a diuretic so that a polyuria develops which tends to maintain the blood chemistry at normal levels. The point, which it is desired to emphasize at this juncture, is that through the establishment of this compensatory polyuria the edema is done away with and, as the older authors rightly observed, the patient is much happier without his bothersome edema.

Miss S. Age 25 B. P. 148/95
Blood Urea N. 12.4 mg. Uric acid 4.0 mg.
Urine Albumin 10 gm. per L., many hyaline casts, a few R. B. C., many leucocytes.
Hemoglobin 70%
Two-Hour Test: while on salt-free diet and fluid intake limited to 800 c.c.

Time	Volume c.c.	Sp. Gr.	NaCl		Urea	
			%	gms.	%	gms.
8.00–10.00	70	1.023				
10.00–12.00	80	1.024				
12.00– 2.00	50	1.030				
2.00– 4.00	70	1.026				
4.00– 6.00	70	1.025				
6.00–10.00	150	1.024				
Total day	490		1.00	4.90	0.7	3.43
Total night	520	1.021	0.88	4.57	1.1	5.20
Total	1010			9.47		8.63

Renal Pathology — marked proteinuria, many hyaline casts, a few red blood cells.
Renal Function — slight impairment (only blood uric acid elevated).
Edema — marked.
Blood Pressure — slightly elevated.
Anæmia — moderate, may be ascribed to long duration of marked albuminuria, more than six years, and not the result of impaired renal function.
Uremia — none.
Diagnosis — Chronic diffuse glomerular nephritis without noteworthy destruction of glomeruli in spite of the fact that marked albuminuria has existed for six years.

TABLE 45. — A case of chronic diffuse glomerular nephritis with a high specific gravity in the urine in spite of the fact that previously retained fluid was being eliminated; this apparent contradiction is due to the fact that the polyuria was of moderate proportions, being only a relative one, since the fluid intake was 800 c.c.; the high salt output, as well as the distinct loss of weight during this period, made it evident that the edema was diminishing; when the edema is lost rapidly and polyuria is present, the urinary specific gravity is low — see tables 42 and 43. The only sign of renal insufficiency is a slight increase in the uric acid of the blood. The considerable variation of specific gravity, 1.021 to 1.030, indicates that there is a normal flexibility of kidney action, and the high level of specific gravity, 1.030, points to a good concentrating power and function of the kidney.

Passive congestion of the kidneys results in oliguria, a urinary specific gravity fixed at a level of 1.020 to 1.025, a high urea and a low salt concentration. These changes are shown in table 46. These urinary findings attributed to passive con-

Successive 24-Hour Specimens of Urine in Patient with Extreme Myocardial Insufficiency

Day	Urine Volume, c.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
1	850	1.022	0.02	0.17	1.76	14.9
2	770	1.022	0.04	0.31	1.74	13.4
3	545	1.025	0.03	0.16	1.56	8.5
4	420	1.025	0.02	0.08	1.56	6.6

Analysis of 24-Hour Samples of Urine in Cases with Less Severe Myocardial Insufficiency

Case	Urine Volume, c.c.	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
1	540	1.020	0.25	1.34	1.44	7.78
2	573	1.019	0.28	1.62	1.76	10.08
3	484	1.022	0.52	2.53	1.58	7.64
4	446	1.018	0.61	2.72	1.38	6.15

Urine in Marked Cardiac Decompensation

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent.	Gm.	Per Cent.	Gm.
8–10	61	1.018	0.20	0.12	1.52	0.93
10–12	52	1.020	0.24	0.12	1.83	0.95
12– 2	65	1.019	0.26	0.17	1.73	1.12
2– 4	55	1.018	0.27	0.15	1.65	0.90
4– 6	30	1.020	0.26	0.07	1.61	0.48
6– 8	35	1.021	0.40	0.14	1.80	0.63
Total day	298			0.77		5.01
Night, 8–8	275	1.021	0.31	0.85	1.85	5.07
Total 24 hours	573			1.62		10.08

Table 46. — Examples of urine analysis in passive congestion of the kidneys. Note: The specific gravity is markedly fixed at a level of about 1.020; there is a diminished output of salt; the low percentage of sodium chloride is very striking and in inverse proportion to the intensity of the passive congestion; the very high concentration of nitrogen (and consequently of the urea) is in distinct contrast with that of the salt; there is marked oliguria.

gestion proved their worth in one interesting case. Two successive two-hour tests from a patient were examined, and both were characteristic of renal congestion. The ward physician sent back word that this was not the correct diagnosis; however, it was shown finally that there was a large mediastinal mass which was impeding the venous return from the kidneys. When the renal circulation is restored to normal, the specific gravity becomes lower, and the urine increases in quantity. The same changes may be noted in the volume and specific gravity of the urine here in association with renal congestion, as in the cases of acute diffuse glomerular nephritis when the edema is being eliminated; these findings have been discussed, and there is no need to repeat them. The blood chemistry may be increased very distinctly when the kidney is the seat of passive congestion; the urea nitrogen in the blood often rises as high as 50 mg. per 100 c.c.; I have seen two cases where kidneys at post mortem examination showed passive congestion only and in which the blood urea nitrogen had reached levels of 78 and 150 mg. per 100 c.c. some time before death. Clinically, it is often very difficult in the course of a chronic nephritis to be certain whether there is cardiac weakness or not; I have seen a number of patients in whom the heart action appeared to be normal, and yet digitalis resulted in marked diuresis, which I interpreted as indicating the existence of distinct cardiac insufficiency that had escaped recognition in the course of a careful physical examination.

A marked *secondary anæmia* frequently is present in cases of chronic diffuse glomerular nephritis. The low colloid concentration of the blood accompanying the anæmia brings about an increased rate of filtration in the glomeruli, resulting in a low fixed specific gravity of the urine (table 47) which simulates

Two-Hour Test for Renal Function

Time	Volume c.c.	Specific Gravity	NaCl		N	
			%	Gms.	%	Gms.
8.00–10.00	150	1.010				
10.00–12.00	166	1.010				
12.00– 2.00	192	1.010				
2.00– 4.00	162	1.010				
4.00– 6.00	200	1.010				
6.00– 8.00	198	1.011				
Total day	1068		0.39	4.06	0.46	4.91
Total night	680	1.010	0.20	1.36	0.52	3.54
Total	1748			5.42		8.45

Table 47. — Low fixed specific gravity in a case of marked anæmia (Hb. 44%; R.B.C. 2,240,000). This may be attributed to a low colloid concentration in the plasma resulting in the filtration of an increased amount of fluid in the glomeruli.

that found in advanced chronic nephritis (Christian[35], Mosenthal[34]). However, a retention of urea nitrogen in the blood does not occur in uncomplicated anæmia. The precise level of hemoglobin or number of red blood cells at which the low fixed specific gravity is inaugurated varies in each case and cannot be stated in exact figures. Undoubtedly, the presence of anæmia may influence the specific gravity findings in chronic diffuse glomerular nephritis but not to as great an extent as might be supposed, because the hemoglobin usually is lower than 50 per cent. when the urine is affected by the anæmia, and this is not the case in chronic Bright's disease unless the nephritis is of a very severe grade when the level of the urea nitrogen in the blood readily reveals the renal insufficiency.

The *renal lesions* of chronic diffuse glomerular nephritis frequently are not accompanied by any apparent diminution of kidney activity whatsoever. It has been difficult to realize that albuminuria, however marked it may be in chronic Bright's disease, is not paralleled by impairment of renal function.

However, this has been established beyond a doubt for very many cases.

The *earliest signs and symptoms* of diminished renal excretory power are an *elevation of the blood uric acid* (table 45) and the presence of *nocturnal polyuria*. It has been mentioned (see table 37) how an isolated rise in the uric acid content of the blood may occur in a number of conditions besides nephritis, but this does not nullify its importance as one of the early signs of impairment of renal function. The presence or absence of a nocturnal polyuria should be ascertained by two distinct steps. First, the history indicates whether or not there are frequent voidings of urine during the night; if these are not present, the night urine is not increased in amount. Second, if the history is positive, it still remains to be determined whether the often repeated voidings at night are the result of nervousness, prostatic hypertrophy or other cause, or are, in reality, indicative of an excess of urinary secretion during the night; this can be done only by actually measuring the amount of urine voided during the hours devoted to sleep. (The upper normal amount of urine voided during the night is usually 400 c.c. or less, though it has been found to be as high as 725 c.c.). Nocturnal polyuria exists in any condition in which there is irritation of the urinary tract (cystitis, pyelitis, etc.) or in any disease accompanied by a compensatory polyuria (diabetes insipidus, polycystic kidney, hypertrophied prostatic gland, etc.) and, therefore, cannot be regarded as pathognomonic of diminished renal function in Bright's disease. At times nocturnal polyuria is not found in chronic nephritis even though there is a distinct impairment of kidney function. In the more advanced cases this is explained easily on the grounds that the patient becomes oliguric in the later stages of the condition, but

in the early periods of the disease it is difficult to account for its absence. In short, the existence of nocturnal polyuria is significant of a compensatory polyuria, but its non-existence does not necessarily indicate that kidney function is normal.

The *second step* in the progressive impairment of renal function in chronic diffuse glomerular nephritis is the *loss of power of the kidney to concentrate* the salt, the urea and other solids in the urine. This impairment of renal function is counterbalanced by a *compensatory polyuria*, whereby the blood is kept comparatively free from the accumulation of urinary excretory products (tables 40 and 48). It is essential to know that this is real y a signal of impaired kidney function. The failure to recognize the presence of such a compensating polyuria may be responsible or the conception that 50 per cent. or more of the kidney tissue must be destroyed before the usual tests indicate any curtailment of renal excretory power.

The *importance of casual specific gravity determinations* in chronic diffuse glomerular and in vascular nephritis cannot be sufficiently stressed. In both of these forms of renal involvement the urine may appear to be normal or unimportant, there may be a trace of albumin, or it may be absent, there may be no casts, or there may be a few of the hyaline variety, and no attention often is paid to a urine whose specific gravity is at the level of about 1.010. I am sure that all of us have seen major operations performed on patients, voiding urines of this description, with disastrous results due to unrecognized renal insufficiency The shortest and safest way to elucidate the real meaning of such low specific gravity readings is to determine the blood urea nitrogen, uric acid and creatinine and the hemoglobin percentage and red blood cell count. It is perfectly possible that the moderate urinary concentration is the result

W. B., Male, age 48.
Blood Pressure — 196/120.
Blood — Urea N. 25.0 mg., uric acid 3.3 mg.
Urine — Album. large amount, many white blood cells, a few red blood cells, a few fine granular casts.
Hemoglobin — 65%
Two-Hour Test for Renal Function: while on usual diet

Time	Volume c.c.	Sp. Gr.	NaCl		Urea	
			%	Gms.	%	Gms.
8.00–10.15	500	1.009				
10.15–12.00	150	1.010				
12.00– 3.25	420	1.010				
3.25– 5.30	290	1.012				
5.30– 7.00	120	1.011				
7.00–10.00	410	1.011				
Total day	1890		0.24	4.54	0.8	15.12
Total night	1200	1.009	0.31	3.72	0.6	7.20
Total	3090			8.26		22.32

Renal Pathology — chronic diffuse glomerular nephritis, associated with considerable arterio- and arteriolosclerosis; secondary contracted kidney.
Renal Function — diminished power to concentrate urea (and other solids); compensatory polyuria, nocturnal polyuria. Blood urea N slightly elevated; specific gravity low and fairly fixed.
Edema — none.
Blood Pressure — markedly elevated.
Anæmia — moderate but distinct.
Uremia — none.

TABLE 48. — Case of chronic diffuse glomerular nephritis illustrating the second step in the progressive impairment of kidney function accompanying this renal lesion; inability to concentrate the urea and other solids in the urine and a counterbalance of this defect by a compensatory polyuria.

of the activity of a normal kidney; on the other hand, it not infrequently is the one readily detected sign of impending retention uremia in an apparently healthy individual. The laboratory worker frequently does not realize the importance of examinations of casual specimens and through careless technique furnishes misleading results that have detracted very largely from the faith physicians in general have in findings of this sort.

The *third and last step* in the progressive diminution of renal activity is reached when the *polyuria changes to normaluria and finally to oliguria.* Under these conditions the specific gravity remains fixed at the same level as when compensatory polyuria existed, that is, at about 1.010, but the quantity of urine is diminished and, as a result, the non-protein nitrogenous constituents of the blood rise (table 49). The grades of impair-

K., Male, age 20.
Blood Pressure — 164/83 to 132/80.
Blood — Sugar .11%, Urea N. 86.2 mg., uric acid 8.3 mg., creatinin 5.0 mg.
Urine — Album. 2.5 gm. per L., a few red blood cells, occasional hyaline casts.
Hemoglobin 35%; *Red Blood Cells*, 2,960,000.
Two-Hour Test for Renal Function: while on usual diet.

Time	Volume c.c.	Sp. Gr.	NaCl		Urea	
			%	Gms.	%	Gms.
8.00–10.00	200	1.010				
10.00–12.00	95	1.010				
12.00– 2.00	100	1.010				
2.00– 4.00	215	1.009				
4.00– 6.00	135	1.008				
6.00–10.00	320	1.010				
Total day	1065		0.29	3.09	0.60	6.39
Total night	140	1.010	0.40	1.64	0.50	2.05
Total	1205			4.73		8.44

Renal Pathology — secondary contracted kidney.
Renal Function — diminished power to concentrate urea and salt; compensatory polyuria replaced by normaluria; blood urea N. and creatinine markedly elevated; specific gravity low and fixed; anæmia marked.
Edema — none.
Blood Pressure — slightly elevated.
Anæmia — marked.
Uremia — no signs at present.

TABLE 49. — Data from a case of secondary contracted kidney; this illustrates the earliest period of the third and final stage in the progressive impairment of renal function that occurs with advancing chronic diffuse glomerular nephritis: the urinary specific gravity is pegged at a level of about 1.010, the volume of urine is not above the average normal, nocturnal polyuria has disappeared and the blood chemistry is decidedly elevated.

ment of renal function as measured by the blood urea nitrogen, etc., are given in table 36. The final diminution in the urine

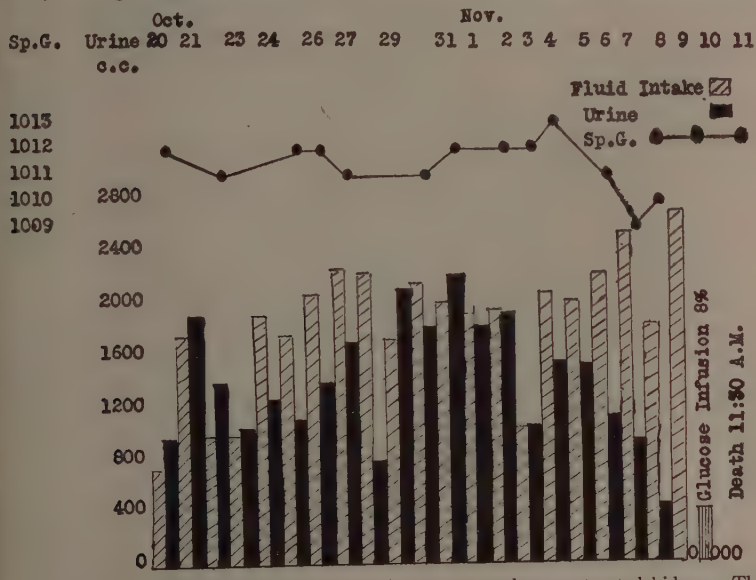

FIGURE 6. Terminal stage in a case of severe secondary contracted kidney. The final progressive oliguria and anuria are the result of overstrain of the glomeruli which consequently exhibit fatigue (oliguria) and at the end cease to function entirely (anuria).

volume usually develops comparatively rapidly after the symptoms of retention uremia have become manifest (fig. 6).

It is true that a high starch, low protein diet will reduce the elevated values revealed by the blood chemistry to a great degree (table 50). This often has been advanced as an argument against the value of these determinations as criteria for the estimation of renal function. It should be recognized that the amounts of uric acid and creatinine in the blood are not greatly modified either by the quantity or the quality of the food consumed. Of these, the creatinine is one of the most valuable indicators of kidney efficiency at our command. The variations to which the urea nitrogen is subject, because of

Before Low Protein Diet		After Low Protein Diet		Author
N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	N. P. N. Mg. per 100 c.c.	Urea N. Mg. per 100 c.c.	
82	67	26	12	Folin, Denis and Seymour.[38]
80	62	44	20	
97	61	22	15	Mosenthal and Lewis.[20]
145	126	32	23	

TABLE 50. — Influence of diet on the blood urea nitrogen; a low protein, high carbohydrate diet may reduce the elevated blood urea nitrogen to normal levels in chronic diffuse glomerular or chronic vascular nephritis; that is, such a diet may nullify the value of blood urea nitrogen as a means of estimating renal function when a secondary or primary contracted kidney exists.

dietary control, seem to me rather exaggerated. The blood urea nitrogen usually is at a characteristic level unless extreme diets have been prescribed, and these generally can be discounted after the patient has been questioned. In doubtful cases further studies of the blood chemistry after the resumption of a normal protein intake, may be indicated.

The treatment accorded the impairment of renal function in chronic diffuse glomerular nephritis has been very much modified since the relation between albuminuria and kidney lesions was recognized by Richard Bright almost a century ago. Until about 1915, every patient with albumin in the urine was subjected to mild or drastic restrictions of the food proteins. The milk and farinaceous diets of that period have been largely forgotten and are rarely ordered. It is difficult to understand why they ever were used. They contain a considerable amount of protein, so that they do not relieve the kidney appreciably from the strain of excreting urea, etc.; they do not furnish enough protein either qualitatively or quantitatively to promote good health and a sense of well-being; they contain an excess

of salts that not only is burdensome to the kidney but aggravates edema and retention uremia; they have a high fluid content that may be an unmanageable load for a failing heart; in short, they do not meet fully the requirements of the sufferer with chronic Bright's disease in any respect and represent a period in medical practice when generous intentions took the place of knowledge, and when it was thought that milk and wheat were nature's best food and that red meats produced hardening of the arteries.

The study of renal function has changed our attitude in regard to the optimal diet in the tubular forms of nephritis (nephrosis), and there is now general agreement that, as long as kidney activity is equal to the task of keeping the body clear of renal excretory products, a high protein diet is not only permissible, but is distinctly indicated. In chronic diffuse glomerular nephritis we have not been as unanimous in formulating our mode of treatment for the patient who shows a slight or no impairment of renal function. Our conclusion that proteins in the dietary injure neither the normal nor the chronically inflamed kidney have been set forth already in chapter XI on the pathology of the kidney. Therefore, we would advocate a diet which contains at least 40 grams of protein daily plus the amount lost in the urine; salt should be restricted, for even a curtailment usually means that 3 to 5 grams a day are being consumed which is sufficient for all purposes. Although sodium chloride in amounts higher than this may do no harm, yet it brings about no benefits, and it may aggravate a uremic or edematous tendency. A considerable quantity of carbohydrates and fats should be insisted on to supplement the 50 grams of protein, more or less, prescribed. A total caloric value of 1,800 to 2,000 usually is sufficient. The quantity of food should be

regulated, if possible, so that the quality of the tissues is maintained as measured by the hemoglobin and red blood cells and that the bulk of the body is neither much below nor above the average normal as determined by weight.

One of the gravest errors that can be made in the treatment of chronic diffuse nephritis is to allow the nutrition of the patient to suffer. It is now appreciated that many of these patients are subject to infections, and often their career is terminated by tuberculous involvement. It is an open question whether some undetermined effect of the albuminuria is responsible for such a clinical course, or whether the overzealous restriction of food proteins has brought about such unlooked for results.

When the usual tests for kidney function show varying degrees of renal insufficiency in chronic diffuse glomerular nephritis, it is a serious problem whether attempts should be made or avoided to maintain the blood urea nitrogen at normal levels or not. If we do follow the impulse to maintain the blood chemistry at normal levels, it must be with the full appreciation of the fact that we are invoking the hazards of malnutrition while attempting to avoid those of retention uremia. We are thus brought face to face with the difficulty of deciding which eventuality will be least harmful to the patient or, possibly looking at the matter in a more hopeful way that, from practical experience, I believe to be justified, which form of dietetic regulation will prolong life more effectively.

Bradford[37] in animal experiments successfully established two facts:

1. By partial nephrectomy as much as $\frac{2}{3}$ of the total kidney weight may be removed apparently without harming the animal; when $\frac{2}{3}$ of the kidney substance has been excised, a considerable and permanent increase in the urine follows.

2. When ¾ of the kidney is extirpated, death occurs in from 1 to 6 weeks from asthenia, accompanied by great wasting but without coma or convulsions.

Especially from the arterial injection studies of Baehr and Ritter[38] and Hayman[39], we are now aware that both in chronic diffuse glomerular nephritis, and in chronic vascular nephritis there is a steady reduction in the amount of functioning cortical tissue terminating in secondary and primary contracted kidneys. The effect of the progress of the pathological lesions of the kidney in chronic nephritis may, therefore, be compared to the symptoms resulting from Bradford's partial nephrectomy experiments. If these two processes are analogous, and I believe that they are, then we are forced to admit that, in treating a condition of impaired renal function in chronic nephritis, we are attempting to influence a symptom, and that we have lost sight of our real object, which is to influence the pathology of the kidney and prevent progress of the renal lesions, if we are able to do so. In other words, it would seem that death accompanying marked renal insufficiency is not dependent upon the elevation of the blood urea or other non-protein nitrogenous substances in the blood, but is the result of asthenia, tissue destruction, anæmia and other processes that are largely beyond our control when 90 per cent. or more of the kidney parenchyma is destroyed.

These problems have been discussed at some length in chapter XI under the heading of treatment of chronic diffuse glomerular nephritis and the conclusion arrived at was that the amount of protein administered should be approximately 40 grams a day plus an amount equal to the quantity of albumin lost in the urine. A diet by which this regime could be carried out also was detailed in the same section.

The three points which it is desired to stress in regard to the therapy of chronic diffuse glomerular nephritis, as governed by the state of renal function, are these:

1. The presence of albumin, casts and red blood cells in the urine, in the absence of compensatory polyuria or an elevation of the blood chemistry, are not to be regarded as indications for bizarre diets that may be considered beneficial for the kidneys, but that will work constitutional havoc with the patient, because they are not adequate to maintaining the integrity of the body tissues. At least 40 grams of protein plus an amount equal to the quantity of albumin lost in the urine should be allowed; the salt should be limited; fluids may be taken as desired.

2. An irksome polyuria, during the day or night or both, often may be set aside by a strict control of the sodium chloride intake and by limiting the proteins, as mentioned in the preceding paragraph. The only means, by which the approximate amounts of salt and of protein actually consumed by the ambulatory patient can be estimated, is the determination of the output of sodium chloride and urea in the 24-hour urinary specimen. It should be remembered that such an increased volume of urine is a compensatory polyuria by which the blood and tissues are cleared of excretory products, and that it should never be remedied by a curtailment of the fluid intake.

3. The diet may be continued as given in section 1 until the urea nitrogen in the blood reaches a level of 40 or at the most 50 mg. per 100 c.c., when the treatment is that for potential retention uremia. That is, the proteins should be decreased, and the starches and the fats of the diet augmented so that the number of calories is maintained at a high level and the destruction of tissue proteins prevented as much as possible.

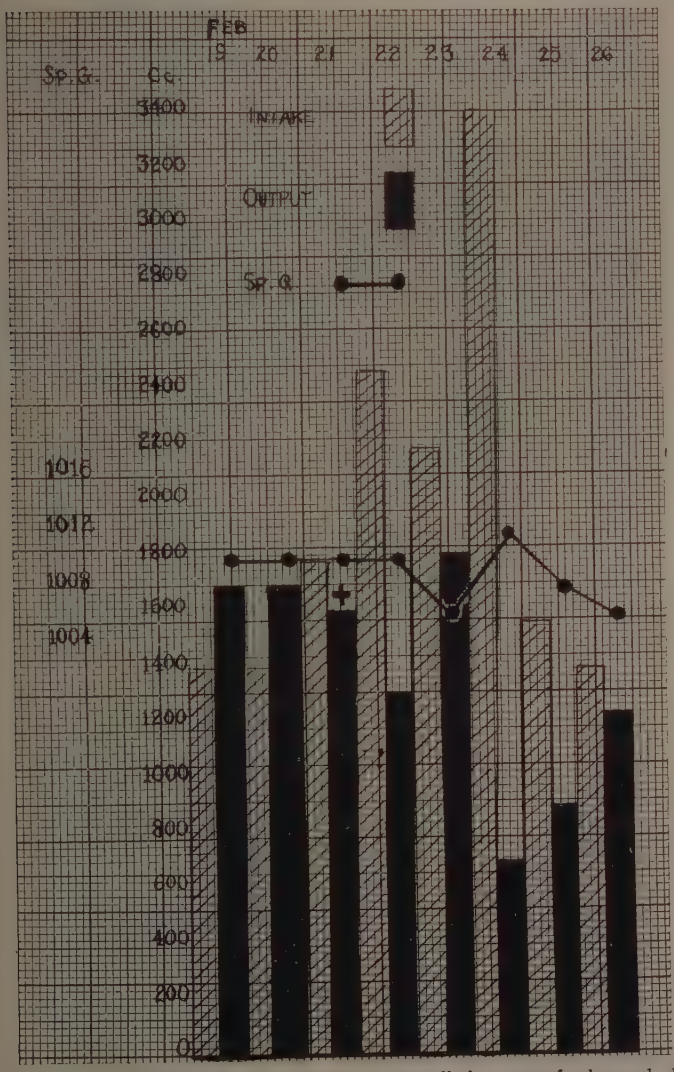

FIGURE 7. — When all of the remaining glomeruli, in cases of advanced chronic nephritis, are constantly functioning at their maximal capacity, the action of diuretic substances is frequently the opposite of what is expected; oliguria comes about, that is, the kidney manifests "fatigue"; in the above case of chronic nephritis, the forcing of water, the blandest of all diuretics, resulted in a diminution of urine, and not in the desired polyuria.

It is in such advanced cases that anæmia becomes manifest, and the patient often may be benefited temporarily by transfusions of blood. The importance of maintaining the compensatory polyuria at this time is really the sheet anchor of treatment. Sometimes the drinking of additional amounts of water is of benefit. However, it must be proceeded with carefully, since in the far advanced cases the kidneys usually are putting forth their best effort, and the patient's sense of thirst is an adequate guide to the optimal quantity of fluid for diuresis. When more water is taken than can be eliminated readily by the renal route, the urine may diminish instead of increasing, thus indicating that the kidney has been overloaded. Such a result is shown in figure 7.

Focal Glomerular Nephritis

Renal function in focal glomerular nephritis, both of the infectious and the embolic variety, is normal in every way. Consequently, there are no clinical signs, and no treatment is necessary for this phase of Bright's disease in these forms of kidney involvement.

This holds true for the focal infectious glomerular nephritis whether of the acute or the prolonged and chronic type. It is possible, though it has not been proved, that such renal lesions. when they become chronic, may gradually assume the pathological aspect found in chronic diffuse glomerular nephritis and finally terminate as secondary contracted kidneys with all the signs and symptoms characteristic of renal function in that condition.

In focal embolic glomerular nephritis the occurrence of signs of impairment of kidney activity, such as a permanent lowering of the specific gravity or elevation of the blood urea nitrogen,

definitely points to the fact that the process in the kidney has changed and that the patient is suffering from an acute diffuse glomerular nephritis progressing into the subacute form which will cause death through renal insufficiency. Baehr and Lande[40] and Baehr[40] are very definite on this point and say that one can be reasonably certain that the intercurrent appearance of symptoms of renal insufficiency in a case of subacute streptococcus endocarditis is not to be ascribed to the embolic glomerular lesions, but that it is evidence of an acute diffuse glomerular nephritis or its sequel, chronic diffuse nephritis. From the cases reported, I should judge that in those instances with a fatal termination through renal insufficiency they were dealing with what has been termed here, subacute diffuse glomerular nephritis. The signs, symptoms and treatment of impaired renal function, under these circumstances, are the same as those previously described under the corresponding headings in this chapter.

Tubular Nephritis

Renal function in tubular nephritis depends more upon the constitutional affections than it does upon the particular lesion in the kidney. This subject will be taken up under the headings as indicated in the discussion of the pathology of this disease in chapter XI.

Albuminous tubular nephritis is an accompaniment of various infections and intoxications. Renal function is not changed from the normal, and no especial therapy is required.

Hypertensive and convulsive tubular nephritis accompanies the toxemias of pregnancy. This disease is so interwoven with the problems of the obstetrician that an adequate presentation of it cannot be attempted within the limits of this book. Conse-

quently, reference is made to appropriate monographs that may clear up this phase of Bright's disease.

Edematous tubular nephritis is characterized by the signs of impairment of renal function incident to the formation and loss of edema as described above, in detail, for acute diffuse glomerular nephritis. Briefly, there is oliguria, a high fixed specific gravity, low concentration of salt and high concentration of urea while fluid is being retained; when edema is being eliminated, the specific gravity becomes lower and the salt output higher. These facts in regard to the specific gravity are shown beautifully in the following case record published by Ohler and Finland[41]:

Dates	*Average Daily Output*	*Specific Gravity*
10/17–10/22	650	1.018–1.022
10/23–10/29	1040	1.015–1.024
10/30–11/2	1375	1.012–1.020
11/3 –11/11	1840	1.003–1.010
11/12–11/21	2060	1.002–1.010
11/21–11/28	2310	1.003–1.006
11/29–12/5	2000	1.004–1.010
12/6 –12/13	1900	1.004–1.010
12/14–12/18	1500	1.005–1.006
12/19–12/25	1400	1.005–1.006
12/26–12/31	1250	1.004–1.006
1/1 – 1/10	2150	1.004–1.006

There is no retention of urea in this condition, and the blood chemistry usually remains normal. In those cases in which the tubular nephritis becomes a diffuse nephritis and the glomeruli are involved, the specific gravity is lowered, and the non-protein nitrogenous constituents of the blood begin to rise in amount; if this process advances, the picture characteristic of a secondary contracted kidney ensues. This differs in no way from that described under chronic diffuse glomerular nephritis. Kaufmann and Mason[42] have noted these findings and call attention to the importance of the observation of the urinary

specific gravity and the blood chemistry in making a diagnosis of the progressive change of tubular nephritis into chronic diffuse glomerular nephritis and, finally, into secondary contracted kidney.

Anuric tubular nephritis, from the clinical point of view, exists only as the result of mercury poisoning, usually brought on by the taking of a considerable quantity of bichlorid of mercury, either accidentally or with suicidal intent. Hitherto, the usual explanation for the diminution in the quantity of urine in this disease has been that the tubules become blocked with detritus derived from the necrosis of the cells lining the tubules. Recently Richards[43] has advanced another theory for the interpretation of the diminished elimination of urine. He finds, and everyone seems to be agreed on this point, that in mercuric chlorid poisoning there is a high glomerular activity. On pathological examination, the glomeruli are certainly free from damage. He explains the lack of urine on the ground of a reabsorption into the blood of the glomerular urine through the damaged tubular epithelium. The thinned out tubular membrane is supposed to absorb the glomerular urine indiscriminately and in large amounts. From the clinical point of view this does not meet all the facts, since there is a low specific gravity even during the oliguric period following suppression of urine in cases of mercury poisoning. Lewis and Rivers[44] obtained a specific gravity of about 1.009 in this stage of the case they report, and the specific gravity did not rise above 1.012, except on one day during the 29 days of observation. If our understanding of the usual process of glomerular filtration and subsequent concentration of the glomerular urine by the tubules is correct, the reabsorption of urine by the tubules in mercuric chlorid poisoning would not seem to be increased but rather

that it was diminished. It would be of great advantage to have these matters cleared up; the treatment accorded this intoxication would be more rational, if we could be sure of the cause of the suppression of urine. Besides the theories mentioned above, there is the idea, which has not been disproved, that constitutional changes bring about a retention of fluid and crystalloids by the body tissues. The symptoms of disturbed renal function in this condition are rapid suppression of urine so that anuria exists on the second, third, or fourth day. Subsequently, the flow of urine is re-established in the cases which recover. Usually patients can tolerate a total cessation of kidney activity for a period of about ten days before they succumb. Accompanying the suppression of urine, the blood chemistry rises rapidly and to very high levels. The one exception is the sodium chlorid content of the plasma which diminishes instead of increasing. In the case of Lewis and Rivers[44], this reached a level of 385 mg. per 100 c.c. (normal values, 580–620). There has been much controversy in regard to the significance of this low chlorid content of the blood plasma; the explanation generally accepted at the present moment, is that it is due to loss of chlorids through vomiting (Trusler, Fischer and Richardson[45]). When the flow of urine is resumed, in favorable cases, the specific gravity is at a low level, pointing to diminished power of reabsorption on the part of the tubules, and the blood chemistry gradually returns to normal.

The symptoms of mercuric chlorid poisoning show that this condition is a constitutional affection and is not a disease confined to the kidneys. There are marked abdominal cramps; there is salivation and moderate stomatitis; there is vomiting and diarrhea, and the pulse is often irregular and weak; the

leucocytes often increase so that the white cell count becomes as high as 40,000 cells per cu. mm. These symptoms occur in addition to those incident to the suppression of urine. It is well known that occasionally death follows within a few hours, or even a few minutes, after the swallowing of bichlorid tablets; such deaths cannot, of course, be explained on the basis of cessation of kidney activity. Kohn[46], in studying this question, has come to the conclusion that these fatalities, that occur before anuria has been established, as well as those that take place after the flow of urine has been resumed, can be accounted for on the basis of a circulatory collapse probably induced by damage to the myocardium. He also mentions the fact that a high number of white blood cells, that is, 30,000 to 40,000 per cu. mm., is an index of the severity of the poisoning and indicates a bad prognosis.

The presence of an ulcerative colitis, without a similar involvement of the remainder of the gastro-intestinal tract, points to the absorption of the mercury and its selective excretion in certain areas. Lieb and Goodwin[47] were able to show that mercury is excreted by the gastric mucous membrane. Because of these facts, that is, the lethal termination due to retention of mercury, and the appearance of mercury in the stomach and large intestine, it has become apparent that gastric lavage and colonic irrigations are an essential part of the treatment for mercurial poisoning.

Vogel's[48] test for mercury is easily carried out and furnishes a ready means of determining whether the mercury has been completely eliminated by the stomach, the intestines and the urine. When a case of mercury poisoning is treated, it should be resorted to systematically as a guide to the therapy.

The treatment for mercuric chlorid poisoning, as advocated

by Lambert and Patterson[49] in 1915, is still the most satisfactory method of therapy. Their mode of procedure is as follows:

The first indication is to give the patient the whites of several eggs and then to wash out the stomach thoroughly. The stomach contents are expressed and examined for mercury, the stomach is thoroughly washed, and a pint of milk introduced. Urine passed spontaneously, or that obtained by catheter, is examined for mercury. The metal appears in the urine in from three to twenty-four hours after it has been swallowed. If more than a day has elapsed since the poisoning occurred, a stool should also be examined for the poison. If the first lavage does not a lay the nausea and vomiting, it is repeated after an hour, and the following routine is begun as soon as the stomach will permit:

1. The patient is given, every other hour, 8 ounces (240 gm.) of the following mixture: potassium bitartrate, 1 dram (4 gm.); sugar, 1 dram (4 gm.); lactose, one-half ounce (15 gm.); lemon juice, 1 ounce (30 c.c.); boiled water, 16 ounces (480 c.c.). Eight ounces (240 c.c.) of milk are administered every alternate hour.

2. The drop method of rectal irrigation with a solution of potassium acetate, a dram (4 gm.) to the pint (500 c.c.), is given continuously.

3. The stomach is washed out twice daily.

4. The colon is irrigated twice daily, in order to wash out whatever poison has been eliminated in that way.

5. The patient is given a daily sweat in a hot pack.

For the less severe cases, a week may be a sufficient time for treatment. When large or successive doses have been taken, or when there is a preëxisting kidney lesion, or when treatment

begins several days after the poison is taken, longer periods of treatment, up to three weeks, are necessary.

Several additions to this treatment have been suggested:

1. Decapsulation of the kidney has been proposed, even before 1915, but has never proved successful.

2. The question of the advisability of giving infusions has been discussed a great deal. Sansum[50] believes that intravenous injections of highly diuretic sugar, salt or alkali solutions were of no benefit and probably shortened life. His observations were carried out on experimental animals. Trusler, et al.[45] conclude that there is some evidence that 2 per cent. salt solution, administered intravenously, may be of some value by forcing the excretion of mercury from the body by way of the kidney. Hayman and Priestley[51] claim that, if urine secretion is not sufficient to furnish a good diuresis when fluid is given by mouth, then intravenous injections of salt solutions should be given 500 to 1,000 c.c. at a time, two or three times a day; in their case they provided 1,650 to 2,790 c.c. of fluid by the venous route in addition to three or four litres of fluid by mouth. It is only fair to state that in their case a diuresis was in progress at the time the intravenous therapy was started.

3. The use of chemical detoxicants, sodium thiosulphate and other antidotes, has not been successful (Sansum[50], Zeigler[52]).

4. Some doubt has been cast on the value of the sweating carried out in Lambert and Patterson's[49] program.

In summary, it may be said that the treatment of Lambert and Patterson can well be adhered to, with the possible omission of the sweating procedures and possibly the addition of intravenous infusions. The statement of Sansum[50] may well be kept in mind that the objects of treatment are: (1) the me-

chanical removal of the poison from the lumen of the alimentary tract; (2) the antidoting of the mercury before it is absorbed.

Arterial Nephritis

Renal Function in Arterial Nephritis. — (Primary involvement of the arteries and the arterioles as discussed in chapter XI. Vascular nephritis, arteriosclerotic nephritis, nephrosclerosis, primary contracted kidney are synonyms). There are two types of arterial nephritis: the first of these is the arterial or arteriolar sclerosis of the renal vessels, the second consists of a necrosis associated at times with an inflammatory reaction, an arteritis and periarteritis. These constitute the so-called benign and malignant forms of nephrosclerosis as described by Fahr and others.

Renal function in sclerosis of the renal arteries and arterioles (benign nephrosclerosis) is the same whether this condition is the result of senile degeneration (decrescent arteriosclerosis) or brought on by the strain of a persistently high blood pressure. The state of renal function in this condition depends upon the permeability of the arteries supplying blood to the glomeruli. If the majority of glomeruli are intact, renal function is normal, but if many are obliterated, the kidney activity diminishes. Thus it is seen that, although the pathological process differs from that in chronic diffuse glomerular nephritis, yet the reasons for impairment of the excretory power of the kidney are the same. The pictures furnished by injection experiments such as those of Baehr and Ritter[38] and Hayman[39] show that the appearance of the persisting arteries and arterioles do not serve to differentiate these two forms of nephritis from one another.

The earliest stages in the impairment of kidney function can be studied in the numerous cases of essential hypertension in which the kidney is only slightly or not at all involved.

The study of renal function has brought out the fact that an elevated blood pressure does not, in every instance, depend upon nephritis, but that the hypertension in itself may be the primary disturbance. The earliest signs in these cases, besides a faint trace of albumin and a few hyalin casts, are an increase in the uric acid content of the blood and a nocturnal polyuria; in other respects the kidney function is normal, as measured by

Mrs. H. Age 60. B.P. 220/140.
Blood — Urea N. 11.2 mg., uric acid 5.2 mg., creatinine 1.6 mg.
Urine — Albumin faint trace, casts none.
Two-hour test while on customary diet.

Time	Volume c.c.	Sp. Gr.	NaCl		Urea	
			%	Gms.	%	Gms.
8.00–10.00	174	1.007				
10.00–12.00	40	1.015				
12.00– 2.00	22	QNS				
2.00– 4.00	48	1.025				
4.00– 7.00	128	1.023				
7.00–10.00	134	1.022				
Total day	546		0.76	4.15	1.2	6.5
Total night	1022	1.012	0.70	7.15	0.6	6.1
Total	1568			11.30		12.6

Kidney lesion — slight or moderate degree of arteriosclerotic kidney.
Blood pressure — distinct hypertension.
Diagnosis — essential hypertension with some secondary arteriosclerosis of the kidney.
Kidney function — increase of the blood uric acid indicating some impairment; there is a distinct nocturnal polyuria which may be set aside if some of the excess salt in the diet is stopped (the larger part of the salt is being eliminated at night); the variation of the specific gravity (18 points) is satisfactory and the maximal concentration of 1.025 indicates good kidney function.

TABLE 51. — Case of essential hypertension with a slight degree of arteriosclerotic kidney, the only indication of impairment of renal function being the blood uric acid and nocturnal polyuria.

the usual criteria of specific gravity and blood urea nitrogen. A case of this sort is given in table 51. Patients exhibiting such a picture of slightly disturbed renal function are very frequently encountered. Usually they do very well, and no dietary or other restrictions are required to control the ne-

J. W., Male, age 32.
Blood Pressure — 210/128.
Blood — Urea N. 105 mg., creatinin 6.7 mg.
Urine — Album. trace, a few fine granular casts.
Hemoglobin 45%; *Red Blood Cells* 2,824,000.
Two-Hour Test for Renal Function: while on usual diet.

Time	Volume c.c.	Sp. Gr.	NaCl		Urea	
			%	Gms.	%	Gms.
8.00–10.00	58	1.011				
10.00–12.00	90	1.010				
12.00– 2.00	92	1.011				
2.00– 4.00	156	1.010				
4.00– 6.00	86	1.011				
6.00– 8.00	110	1.011				
Total day	592		0.34	2.01	1.1	6.47
Total night	1250	1.010	0.49	6.18	0.9	11.13
Total	1842			8.19		17.60

Renal Pathology — primary contracted kidney.
Renal Function — specific gravity of the urine is low and markedly fixed; retention of urinary excretory products as shown by very high figures for the blood urea and creatinin; the nocturnal polyuria still persists as a sign of ineffective compensatory polyuria; a maximal degree of impairment of renal function.
Edema — none.
Blood Pressure — marked elevation of both the systolic and diastolic pressures.
Anæmia — marked.
Uremia — no signs at present.

TABLE 52. — Data from a case of advanced arterial nephritis, primary contracted kidney. The findings are very much like those in secondary contracted kidney: there is a secondary anæmia, the specific gravity is low and fixed, and the blood chemistry is distinctly elevated. In both instances the changes from the normal are brought about by the obliteration of the circulation within the glomeruli. The more marked elevation of blood pressure and the smaller amount of albumin in the contracted kidney of arterial origin, as compared to that resulting from a chronic inflammatory process, are characteristic, but not constant, and consequently not reliable guides in differential diagnosis.

phritis. The arterial nephritis progresses so slowly that in a person of middle age or over it has little menace. This does not mean, of course, that there should be no effort made to treat the cause of the sclerosis of the arteries whether it be blood pressure, or lead poisoning or something else, because even if the kidneys are only slightly affected other tissues in the body may not fare so well.

It has been shown previously in the section on blood pressure in this volume that while only about 10 per cent. of the cases of essential hypertension ever develop a serious degree of vascular involvement of the kidney, this possibility must not be ignored, and the only means of determining the progress of the nephritis is through tests for renal function. The arteriosclerosis in the kidneys develops slowly as a rule, and by gradual stages the blood supplied to the glomeruli is cut off and renal function is diminished until the excretory activity of the kidneys is no longer adequate. Then the specific gravity of the urine becomes low and fixed, and the blood chemistry is distinctly elevated (see table 52). These findings are exactly like those of chronic diffuse glomerular nephritis in the advanced stages, and it is often impossible to make a differential diagnosis between the two.

The treatment that should be accorded the impaired kidney function in arterial nephritis is exactly similar to that resorted to in handling the disfunction of chronic diffuse glomerular nephritis; this has been outlined in the preceding sections, and there is no necessity for repeating it at this point.

When patients are afflicted with arterial nephritis or any condition in which a marked arterial hypertension is present, it is necessary to be on the constant lookout for myocardial insufficiency. When the kidney becomes congested, there are

certain signs of impaired renal function that manifest themselves. Thus there may be two factors that influence renal activity. The interpretation of the signs may, at times, become exceedingly difficult. The signs and symptoms incident to passive congestion of the kidney and their treatment have been discussed previously. They vary in no manner in arterial nephritis from those in uncomplicated passive congestion or in myocardial failure associated with chronic diffuse glomerular nephritis.

Arteriolar Necrosis of the Kidney

Renal function in arteriolar necrosis of the kidney (malignant sclerosis). — Necrosis of the renal arterioles comes on suddenly in patients who have had hypertension for a long period with both elevation of the diastolic as well as the systolic pressure. There is a rapid onset of marked renal insufficiency, which results in death through retention uremia within a brief period. The signs of maximum impairment of renal function come on; especially noted is the concentration of blood urea nitrogen at a level of 100 mg. per 100 c.c. or higher. Death because of renal insufficiency occurs in from five days to five months after the onset. These facts are taken from the report of Klemperer and Otani[53]. I have seen only one such case, and the findings harmonized in all respects with the facts furnished by these authors.

The treatment of this condition is symptomatic only. There is no known method by which the necrotic processes in the blood vessels may be controlled, and consequently it seems useless to insist too strongly upon measures to curb an elevated blood urea that can accomplish little or nothing toward a prolongation of the patient's life.

Bibliography

1. Richards, A. N.: Nature and mode of regulation of glomerular function, Am. Jour. Med. Sc., **170**: 781, 1925.
2. Marshall, E. K., Jr.: The secretion of urine, Physiol. Rev., **6**: 440, 1926.
3. Rowntree, L. G. and Geraghty, J. T.: The phthalein test, Arch. Int. Med., **9**: 284, 1912.
4. Rowntree, L. G. and Fitz, R.: Studies of renal function in renal cardio-renal and cardiac diseases, Arch. Int. Med., **11**: 258, 1913.
5. Tileston, W. and Comfort, C. W.: The total non-protein nitrogen and the urea of the blood, and the phenolsulphonephthalein excretion in children, Am. Jour. Dis. Child., **10**: 278, 1915.
6. Hill, L. W.: Studies in the nephritis of children, Am. Jour. Dis. Child., **17**: 270, 1919.
7. Addis, T.: Renal function and the amount of functioning tissue, Arch. Int. Med., **30**: 378, 1922.
8. Austin, J. H., Stillman, E. and Van Slyke, D. D.: Factors governing the excretion rate of urea, Jour. Biol. Chem., **46**: 91, 1921.
9. Möller, E., McIntosh, J. F. and Van Slyke, D. D.: Studies of urea excretion. II. The relationship between urine volume and the rate of urea excretion by normal adults, Jour. Clin. Invest., **6**: 427, 1928.
10. MacKay, E. M. and MacKay, L. L.: The relation between the blood urea concentration and the amount of functioning renal tissue, Jour. Clin. Invest., **4**: 127, 1927.
11. Möller, E., McIntosh, J. F. and Van Slyke, D. D.: Studies of urea excretion. IV. Relationship between urine volume and rate of urea excretion by patients with Bright's disease, Jour. Clin. Invest., **6**: 485, 1928.
12. Foster, N. B.: Renal function in persons having only one kidney, Arch. Int. Med., **36**: 884, 1925.
13. Chace, A. F. and Myers, V. C.: The value of recent laboratory tests in the diagnosis and treatment of nephritis, Jour. Am. Med. Assoc., **67**: 929, 1916.
14. Myers, V. C., Fine, M. S. and Lough, W. G.: The significance of the uric acid, urea and creatinine of the blood in nephritis, Arch. Int. Med., **17**: 570, 1916.
15. Fishberg, A. M.: The interpretation of increased blood uric acid in hypertension, Arch. Int. Med., **34**: 503, 1924.
16. Behre, J. A. and Benedict, S. R.: Studies in creatine and creatinine metabolism, Jour. Biol. Chem., **52**: 11, 1922.

17. Myers, V. C. and Lough, W. G.: The creatinine of the blood in nephritis: its diagnostic value, Arch. Int. Med., **16**: 536, 1915.
18. O'Hare, J. P.: Compatibility of long life with low renal function, Jour. Am. Med. Assoc., **73**: 248, 1919.
19. MacKay, E. M. and MacKay, L. L.: The concentration of urea in the blood of normal individuals, Jour. Clin. Invest., **4**: 295, 1927.
20. Mosenthal, H. O. and Lewis, D. S.: A comparative study of tests for renal function, Jour. Am. Med. Assoc., **67**: 933, 1916.
21. McQuarrie, I. and Whipple, G. H.: Renal function influenced by intestinal obstruction, Jour. Exper. Med., **29**: 397, 1919;
Lauria, W. H.: The blood urea nitrogen in acute intestinal obstruction, Arch. Int. Med., **27**: 620, 1921;
Tucker, W. J.: Uremia following gastro-enterostomy, Wisconsin Med. Jour., **20**: 528, 1922;
Brown, G. E., Eusterman, G. B., Hartman, H. R. and Rowntree, L. G.: Toxic nephritis in pyloric and duodenal obstruction, Arch. Int. Med., **32**: 425, 1923;
Orr, T. G. and Haden, R. L.: Chemical changes in the blood of the dog in experimental peritonitis, Jour. Exper. Med., **48**: 339, 1928;
Haden, R. L and Orr, T. G.: Chemical findings in the blood of the dog after temporary obstruction of the pylorus, Jour. Exper. Med., **48**: 591, 1928.
22. Schmitz, H. W.: Comparative concentration of urea in the blood and saliva in a series of pathologic cases, Jour. Lab. and Clin. Med., **8**: 78, 1922.
23. Hench, P. S. and Aldrich, M.: A salivary index to renal function, Jour. Am. Med. Assoc., **79**: 1409, 1922.
24. Hench, P. S. and Aldrich, M.: A salivary index to renal function, Jour. Am. Med. Assoc., **81**: 1997, 1923.
25. Stealy, C. L.: The clinical value of the salivary urea index, Jour. Lab. and Clin. Med., **14**: 162, 1928.
26. Pratt, J. H.: The dilution and concentration test, Boston Med. and Surg. Jour., **195**: 203, 1926.
27. Volhard, F. and Becher, E.: Die klinischen Methoden der Nierenfunktionsprüfung, Urban and Schwarzenberg, 1929.
28. Rosenberg, M.: Die Klinik der Nierenkrankheiten, S. Karger, Berlin, 1927.
29. Fishberg, A. M.: Hypertension and Nephritis, Lea and Febiger, Philadelphia, 1930.
30. Mosenthal, H. O.: Renal function as measured by the elimination of fluids, salt and nitrogen, and the specific gravity of the urine.

The application of the method to ambulant patients, Med. Clin. N. America, **4**: 209, 1920.

31. MacLean, H.: Modern Methods in the Diagnosis and Treatment of Renal Disease, Lea and Febiger, Philadelphia, 1927.
32. King, S. E.: The urea tolerance test, Arch. Int. Med., **42**: 877, 1928.
33. Hedinger, M. and Schlayer, K.: Ueber die Prüfung der Nierentätigheit durch Probemahlzeit, Deutsch. Arch. f. klin. Med., **114**: 129, 1914.
34. Mosenthal, H. O.: Renal function as measured by the elimination of fluids, salt and nitrogen and the specific gravity of the urine, Arch. Int. Med. **16**: 733, 1915; The effect of high, low and normal diets, Arch. Int. Med., **22**: 770, 1918. Value of tests for renal function, Ohio State Med. Jour., **18**: 348, 1922.
35. Christian, H. A.: The renal function in pernicious anemia, Arch. Int. Med., **18**: 429, 1916.
36. Folin, O., Denis, W. and Seymour, M.: The non-protein nitrogenous constituents of the blood in chronic vascular nephritis (arteriosclerosis) as influenced by the level of protein metabolism, Arch. Int. Med., **13**: 224, 1914.
37. Bradford, J. R.: The results following partial nephrectomy and the influence of the kidney on metabolism, Jour. Physiol., **23**: 415, 1899.
38. Baehr, G. and Ritter, S. A.: The arterial supply of the kidney in nephritis, Arch. Path., **7**: 458, 1929.
39. Hayman, J. M., Jr.: Experiments on the patency of the blood vessels of nephritic kidneys obtained at autopsy, Jour. Clin. Invest., **8**: 89, 1929.
40. Baehr, G. and Lande, H.: Glomerulonephritis as a complication of subacute streptococcus endocarditis, Jour. Am. Med. Assoc., **75**: 789, 1920;
Baehr, G.: The significance of the embolic glomerular lesions of subacute streptococcus endocarditis, Arch. Int. Med., **27**: 262, 1931.
41. Ohler, W. R. and Finland, M.: Nephrosis, Med. Clin. of N. America, **13**: 139, 1929.
42. Kaufmann, J. and Mason, E.: Nephrosis, Arch. Int. Med., **35**: 561, 1925.
43. Richards, A. N.: Methods and Results of Direct Investigations of the Function of the Kidney, Baltimore, 1929.
44. Lewis, D. S. and Rivers, T. M.: Chemical studies on a case of bichlorid poisoning, Bull. Johns Hopkins Hosp., **27**: 193, 1916.
45. Trusler, H. M., Fisher, W. S. and Richardson, C. L.: Chemical

changes in the blood in mercuric chlorid poisoning, Arch. Int. Med., **41**: 234, 1928.

46. Kohn, L. A.: Acute mercuric chlorid poisoning, Arch. Int. Med., **37**: 225, 1926.
47. Lieb, C. C. and Goodwin, G. M.: The excretion of mercury by the gastric mucous membrane, Jour. Am. Med. Assoc., **64**: 2041, 1915.
48. Vogel, K. M. and Lee, O. I.: Detection of mercury in the excretions, Jour. Am. Med. Assoc., **62**: 532, 1914.
49. Lambert, S. W. and Patterson, H. S.: Poisoning by mercuric chlorid and its treatment, Arch. Int. Med., **16**: 865, 1915.
50. Sansum, W. D.: The principles of treatment in mercuric chlorid poisoning, Jour. Am. Med. Assoc., **70**: 824, 1918.
51. Hayman, J. M., Jr. and Priestley, J. T.: The importance of diuresis in the treatment of certain cases of mercuric chlorid poisoning, Am. Jour. Med. Sc., **176**: 510, 1928.
52. Zeigler, W. H.: A study of the efficiency of certain antidotes in the treatment of acute bichlorid of mercury poisoning, Jour. Lab. and Clin. Med., **10**: 59, 1925.
53. Klemperer, P. and Otani, S.: Studies in "malignant sclerosis" of the kidneys (Fahr), Arch. Path., **8**: 559, 1929.

CHAPTER XIII

EDEMA IN BRIGHT'S DISEASE

(Pathological Physiology, Symptoms, Signs, Treatment)

In collaboration with James J. Short and S. Edward King

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Pathological Physiology, Symptoms and Signs

In collaboration with James J. Short

Foreword

The pathological physiology of the accumulation of fluid in the subcutaneous tissues and in the body cavities, the peritoneum, the pleura and the pericardium, has not been elucidated completely. Doubtless, there are at least two distinct types of edema, that occurring in the various forms of diffuse glomerular nephritis and that found in the edematous tubular nephritis (lipoid nephrosis). The two may be found combined

in the same case as indicated by the name "glomerular nephritis with a nephrotic component". From the clinical aspect, two points of diagnostic value in regard to the edema of Bright's disease, are to be mentioned here. In the first place we have noted for some years that when the body cavities are subject to distention with fluid in Bright's disease, it is the peritoneal space that is invariably the first site of the edematous accumulation and continues predominant throughout; the frequency of infection of this peritoneal fluid in edematous tubular nephritis suggests a greatly depressed functional activity and vulnerability in the lymphatic and vascular apparatus supplying the peritoneum; when anasarca is the result of cardiac failure the pleura inevitably shows the first accumulation of fluid, and the peritoneum follows. This predominance of ascites over hydrothorax or vice versa has furnished invaluable information in diagnosing the rôle of the heart and of Bright's disease in cases where both were factors. In the second place there is the well known, and generally appreciated, fact that the edema of Bright's disease is not first seen in the dependent parts, as in passive congestion, but is prone to make its initial appearance about the face. This phenomenon, and the fact that the edema frequently precedes the advent of albuminuria, indicate that the fluid retention in Bright's disease is not entirely due to the inability of the kidney to excrete water but is associated with physical and chemical disturbances in the blood, the lymph, the capillaries and the soft tissues.

Limitation of space forbids a complete analysis in the section which follows, of the physiology and pathology of fluid regulation. This has had to be curtailed very much, but it is hoped that all the facts of clinical importance have been pre-

sented, thus fulfilling the real purpose of this book. For a detailed discussion of the pathological physiology of edema the reader is referred either to the monograph of McLean[1] or that of Elwyn[2].

Physiology and Pathology of Fluid Regulation

Intra-capillary Blood Pressure

The intra-capillary blood pressure has a direct bearing upon the amount of fluid that passes through the capillary wall into the surrounding spaces and tissues. The problem of edema would be extremely simple, if this were the only factor concerned; the effect of the intra-capillary vascular tension, however, is modified by the osmotic pressure of the plasma proteins, the permeability of the capillary wall, the dilution of the blood, etc., all of which have to be duly considered in explaining the movement of fluid into the extra-vascular territory which results in the formation of edema. Boas in the section on capillary pressure in the first half of this book has given the salient facts on this subject, and they may be reviewed here.

The capillary blood pressure represents the head of pressure of the blood in the capillaries. It is composed of two elements, the pressure generated by the heart beat and transmitted through the arterial tree, and the hydrostatic pressure determined by the height of the column of blood between the level of the heart and the particular part of the body that is being studied. The blood pressure gradually diminishes from the heart towards the periphery, that is, the capillaries. The chief drop occurs in the arterioles before the capillaries are reached. The capillary blood pressure ranges between ten and twenty-five millimeters of mercury and is changing constantly; it fluctuates according to the degree of contraction of the arterioles.

Since it depends upon the activity of these structures, it varies greatly in the different areas supplied by the individual arterioles. The capillary pressure is, therefore, to a great extent, independent of the general arterial pressure.

This capillary blood pressure is the filtration pressure which directs, so to speak, the passage of water from the blood to the tissues. If a person stands quietly for a long time with hands hanging at the side, there will be considerable swelling of both hands and feet. This is due to the effect of the hydrostatic pressure of the column of blood extending from the heart to the dependent part. Kylin[3] found high capillary pressure in patients with acute diffuse glomerular nephritis. This he regards as a sign of diffuse capillary inflammation. Others have been unable to confirm Kylin's observations. Hence, the significance of the capillary pressure in the edema of acute nephritis has not been settled satisfactorily. In patients with cardiac insufficiency, even when the venous pressure is elevated, the capillary pressure is normal or low. Hence reasons other than increased pressure within the capillaries must be sought as a cause for the edema of passive congestion. The capillaries become dilated, possibly due to lack of oxygen, and their walls become more permeable and so favor the formation of a filtration edema.

Permeability of the Capillary Wall

The capillary wall interposes a single layer of epithelial cells between the blood and the surrounding tissue fluid; it acts as a simple filter and has no secretory powers. It has been shown that there are certain physical differences between dead and living membranes as regards the process of diffusion, but the capillary membrane remains entirely passive and responds like a

filter to the extra- and intra- capillary influences; this holds true under normal conditions as well as when edema is being formed.

Since capillaries are semi-permeable membranes they readily permit the passage of *water*, dissolved gases and *crystalloids* of small molecular structure (urea, glucose, etc.); larger molecules pass through more slowly, if at all, while *colloids* are scarcely diffusible under normal conditions. It is principally the *proteins*, through their colloid osmotic pressure, which are responsible for the maintenance of the fluid volume within the capillaries. If they were not present, the intra-capillary blood pressure of 25 to 30 mm. of mercury would force all the fluid portion of the blood through the capillary walls.

Colloids and non-diffusible electrolytes exert a definite influence upon the distribution of extra-capillary ions because of the difference of electrical potential on the two sides of the capillary membrane. This influence is often referred to as the *Donnan phenomenon* or equilibrium, from F. G. Donnan[4], who, in 1911, derived a formula expressing this influence quantitatively. McLean points out that the principle of Donnan must be evaluated with much caution, when applied to a living organism, because the factors involved are constantly in a state of flux and true equilibrium is never attained as is the case with *in vitro* experiments. The condition obtaining *in vivo* is sometimes referred to as a "dynamic equilibrium"; for this reason all the factors concerned in fluid exchange through the capillary wall are difficult of separate quantitative determination.

Capillary permeability is very variable even under normal conditions. Our knowledge concerning the physiological processes which control it is practically confined to the one fact,

though there are doubtlessly many other such influences, that *dilation of the capillaries* results in greater permeability. Thus Krogh[5] found that dilated capillaries allowed soluble starch to pass through their walls, which did not occur under ordinary circumstances. Krogh has shown that the caliber of individual capillaries varies from time to time depending largely upon the needs of the surrounding tissues. The mechanism of such activity is none too clear. Aside from the intra-capillary blood flow and blood pressure, controlled by the arterioles, as previously mentioned, the contractile Rouget cells are undoubtedly important factors. Krogh's masterful researches have established many facts concerning these interesting structures. They are distinct from the endothelial cells of the capillary wall, have muscular properties, are spider shaped and branching, are innervated and doubtlessly under nervous control. In addition their tone is influenced greatly by the posterior pituitary hormone, since Krogh has produced edema in the frog through probable relaxation of the Rouget cells by extirpation of this structure.

Injury of the capillary walls may render them permeable to proteins. This has been recognized for a long time as one of the possible factors in the production of edema. Alcohol, mercuric chloride, oxygen deprivation according to Landis[6], arsenic according to Freund[7], iodine and exposure to sunlight according to others, all injure the capillary wall in such a way that proteins may pass through it. The influence of lack of oxygen in the production of cardiac edema has been noted already. The possibility of a universal capillaritis in those edematous forms of Bright's disease, which have been induced by the injurious action of bacterial products, is acknowledged generally but not proved.

Colloids

In any discussion of edema the water-binding properties of the tissues must be taken into consideration. Protoplasm is a colloid and as such is subject to the laws which govern colloidal behavior. The colloidal system of protoplasm is made up of particles of proteins, nucleoproteins, lipoids and electrolytes (the dispersed phase) suspended in an aqueous solution of electrolytes and some proteins (the continuous phase). The particles of a colloidal system are similarly charged, and in alkaline solutions, such as the body fluids, these charges are negative. Since similar charges repel one another there is dispersion of particles. Neutralization of the charges by the introduction of oppositely charged ions of electrolytes or the passage of an electric current will cause agglutination of particles; this causes freeing of a certain amount of the water bound in the colloidal system.

Swelling of the particles by the taking up of water (imbibition) is a property of all colloids. Since weak acids have been shown to cause a maximum rate of swelling, it has been assumed that a change in the hydrogen ion concentration of the blood toward the acid side might explain edema. The very small range of fluctuation in the hydrogen ion concentration of the blood and tissue fluids, possible during life, makes this explanation untenable.

Colloid osmotic pressure and total surface area of the suspended particles vary inversely as the size of the particles. This fact has an important bearing on the edema of nephrosis, where the small albumin particles have been replaced by the larger globulin particles and the still larger particles of the lipoidal substances. Certain electrolytes have the ability to change the

electric charges of the particles, which in turn causes their agglutination and the freeing of water. Colloids present no obstacle to the free diffusion of electrolytes but are generally quite impermeable to other colloids.

Colloids have the ability to fix varying quantities of water, but certain electrolytes may profoundly affect their capacity for hydration; many diuretic substances probably exert their effect in this way rather than by direct action on the kidneys.

Electrolytes

Sodium Chloride. — Widal and Javal[8] and Strauss[9], about 1902, discovered that the edema of Bright's disease could be made to appear and disappear with the alternation of salt-containing and salt-free diets. The same relation between water retention and sodium chloride intake exists, to a certain degree, in normal persons and is marked in cases of cardiac insufficiency. This originally led to the conclusion that edema was the result of a water retention made necessary to keep the sodium chloride, which the kidney failed to eliminate, in a solution of physiological concentration. While the edema can be controlled in some patients with the ease and precision of treatment seen in the original case of Widal and Javal, unfortunately this has not held true for all instances, and it has become apparent that, though salt retention is, at times, the dominating influence in the production of edema, in many subjects it is not the controlling factor.

Retention of sodium chloride may occur without the production of edema as measured either by increase of weight or the usual physical signs of subcutaneous swelling or pitting. (It is known that about six liters of excess fluid may be retained before edema becomes manifest.) Salt retention takes place

notably in the advanced instances of primary and secondary contracted kidney, when the renal function has been impaired to such a degree that the elimination of salt has been curtailed. This constitutes the so-called "dry chloride retention" of the older French authors. Mechanical obstruction of the urinary passages by calculi, new growths, stricture, etc., also will result in salt retention without production of edema. Fishberg[10] cites two such cases with a sodium chloride plasma concentration, about double the normal, of 1100 and 930 mg. These and other observations indicate that an excess of salt in the body is not the only factor necessary to produce edema, though it is a very important link in the chain of the pathological physiology of edema formation. It must be remembered also that fluid may be held back and edema produced even when there is no impairment of renal capacity for excretion of sodium chloride.

The element in sodium chloride favoring the production of edema has been shown to be the sodium and not the chlorine. The very delicate balance within the organism of the effects of the various salts may be gathered from a few facts that have considerable clinical importance. Whereas sodium favors the retention of fluid, potassium does not; sodium salts other than sodium chloride, such as bicarbonate or bromide of sodium, have the same tendency as sodium chloride while potassium, ammonium and calcium chloride have actually become recognized as diuretics. The use of "substitute salts" in edematous nephritis should exclude those containing sodium.

Sodium chloride is not diffused evenly throughout the body fluids, but about two-thirds of that contained in the body is stored in the muscles, intestines and skin; of these reservoirs the skin contains the greatest concentration, but the muscles hold the greatest total amount because of their great bulk.

Calcium is known to exert a definite anti-edemic influence. Cantarow and Gordon[11] concluded that it may replace sodium, which has accumulated in the tissues, and decrease the affinity of the tissue colloids for water; Fischer[12] found that calcium-protein compounds have a lower capacity for hydration than sodium-protein compounds; Leo Loeb[13] states that calcium ions tend to make the capillaries impermeable, though potassium ions tend to have the opposite effect. He further states that sodium increases permeability of a cell membrane, and that whereas calcium has a hardening effect on colloids, sodium and potassium have a dissolving or softening effect. Calcium salts given orally sometimes effect a rapid discharge of renal edemas in certain cases where other means have been found ineffective (Hulse[14]).

Proteins of the Blood Serum

The proteins of the blood serum have, within recent years, come to be recognized as one of the principal factors in the production of edema. The serum proteins are so large in their molecular structure that they do not pass through the capillary wall as the smaller crystalloid bodies do. Consequently the *osmotic pressure*, which the proteins exert, constantly tends to attract fluid into the lumen of the capillaries. Starling[15], as long ago as 1896, established the fundamental fact that the osmotic pressure of the blood proteins is about 30 mm. of mercury, which is the approximate equivalent of the intra-capillary pressure, and thus these two forces counterbalance one another in maintaining the proper blood volume and prevent undue accumulation of fluid in the extravascular spaces.

The *amount of serum proteins* present necessarily influences the osmotic pressure which these substances exert. The osmotic

pressure apparently diminishes much more rapidly than a direct ratio with a lowered blood protein would indicate (Fishberg[16]). This element in the situation is doubtless a great factor in the production of the edema so characteristic of edematous tubular nephritis (chronic nephrosis). As given in table 31, from Epstein's investigations, the normal total protein of the blood serum was 7.4 grams per 100 c.c., while that in cases of edematous tubular nephritis was only about one half as great, being 3.9 grams per 100 c.c.

The *kind of serum proteins* present in the blood also has a great bearing on the height of the osmotic pressure exerted. This quality of the proteins depends upon their molecular size. According to Cohn, Hendry and Prentiss[17] the minimum molecular weight of serum albumin is approximately 45,000, while that of pseudoglobulin is 81,000 and of euglobulin 135,000. The smaller the molecule is, the greater is its osmotic pressure in proportion to its percentage in the blood plasma; in other words, since in edematous tubular nephritis there is a very great loss of serum albumin, with its smaller molecule as compared to the larger globulin complex (see table 31, also discussion in chapter XI), the osmotic pressure is considerably diminished and the production of edema, through the increased passage of fluid to the extra-capillary areas, is distinctly favored.

The experiments of Leiter and McLean[18], in which they effected edema in dogs by copious bleeding, reinjecting the blood cells but not the plasma, prove in a practical way the truth of the statements made in the previous paragraphs regarding the rôle of the plasma proteins in the production of edema for which Epstein has pleaded for a long time. Independent work by Barker and Kirk[19] is also in harmony with

these findings. In their experiments, blood was removed at intervals from animals, and the corpuscles returned to the circulation, suspended in a protein-free isotonic medium. They found that the resulting edema increased when the albumin dropped below one gram per 100 c.c. and diminished when it rose above this amount.

Central Nervous System Regulation

A central nervous system control and regulation of fluid distribution is now believed in by many investigators and writers. This has been championed notably in Elwyn's[2] volume on edema. A cerebral center probably exists in the *hypothalamus;* direct evidence for this has been found in post-mortem examinations in which lesions were present in an area adjacent to the hypophysis, but with the latter structure intact. These cases, during life, showed chronic polyuria. A similar diuresis has been produced experimentally in animals by mechanical injury to an area in the para-infundibular region somewhat above that punctured by Claude Bernard for the production of glycosuria. Of interest in this connection is the experiment by Marx[20] who produced a blood dilution curve and diuresis during deep hypnosis by the suggestion of drinking.

Endocrine Factors

In close anatomic and physiologic relationship to the fluid regulating center of the hypothalamus is the *pituitary gland.* Even though the hypophysis can be removed completely without producing diuresis, yet the antidiuretic effect of pituitary extract injections in diabetes insipidus is well known and universally successful. Nerve fibres have been demonstrated, which connect the posterior and the middle lobes of the pituitary

gland with the hypothalamic center, indicating the probability of a co-ordinated action between them in the regulation of fluid distribution. Apparently the middle and posterior lobes of the pituitary gland are concerned chiefly in fluid regulation. The initial effect of the active principle is a diuresis, which is followed by a much more prolonged oliguria.

Thyroid substance has long been known to increase the rate of water elimination, while hypothyroidism leads to myxedema. Thyroid extract has been employed extensively by Eppinger[21] and by Epstein[22] in the treatment of edema. It seems most probable that it exerts this influence by increasing the body's total metabolism, and thus freeing water bound by colloids. The influence of thyroid on calcium mobilization must be considered also, since Aub[23] reports that thyroid extract increases calcium excretion far in excess of acids or the parathyroid hormone.

Parathyroid extract likewise influences water exchange, which probably is due indirectly to its effect on calcium metabolism.

Diminished Kidney Function

Inability of the kidney to eliminate urine (oliguria or anuria) was regarded originally as the cause of edema. This was at the time when Bright's disease was diagnosed as nephritis, and all the symptoms of this condition were considered to be secondary to changes in renal function. We now know definitely that anuria may persist with no curtailment of fluid intake for about ten days, as a rule, before death ensues (though a period of thirty has been recorded by Myers[24]), and yet edema does not develop to a noticeable extent. It may be that the skin, the lungs and the intestines, which ordinarily eliminate forty per cent. of the water that the body excretes, become more active

and vicariously throw off the accumulating burden of water. It becomes obvious that the chemical changes in the blood and the structural pathology in the capillary walls, the surrounding tissues and the nervous system are responsible for edema, and that inability of the kidney to eliminate water, as far as edema and anasarca are concerned, is only a secondary effect since the fluid is not presented at the renal excretory channel but is held back in the intercellular tissues.

Blood Volume and Hydremia

As might be expected from the facts detailed in the last paragraph an *increased blood volume* has not been found in cases of Bright's disease, whether accompanied by edema or not (Brown and Rowntree[25]). In 1877 the possibility of *hydræmic plethora* as a causative factor in the production of edema was investigated painstakingly by Cohnheim and Lichtheim[26]. They came to a negative conclusion. The explanation of the apparent watery dilution of the blood occurring in the edematous forms of Bright's disease now clearly appears to be the result of the loss of albumin in the urine, and it is the lowered concentration of albumin in the blood serum that is responsible for the production of the edema, and not the hydremia which is only an inevitable sign of the protein loss from the blood.

Edema of the Various Forms of Nephritis

Acute Diffuse Glomerular Nephritis

Edema is a frequent and characteristic symptom of acute diffuse glomerular nephritis; however, there are many cases in which edema does not occur, and these often escape diagnosis unless a blood-tinged urine or a casual urinary examination

calls attention to the condition. The extent and intensity of the edema vary a great deal; it may be only slight and confined to the subcutaneous tissues, or it may be a true and marked anasarca, almost doubling the body in weight, associated with the accumulation of large amounts of fluid not only in the tissues but also in the body cavities, notably the peritoneal and pleural spaces. Puffiness about the eye-lids may be the first symptom; this is noticed especially upon awakening in the morning. The edema usually manifests itself rapidly without warning and without any accompanying subjective symptoms. Face, hands, upper and lower extremities, back, in fact, the subcutaneous tissues of the entire body, may be more or less involved. Such a pitting edema often imparts a peculiar wax-like, translucent appearance to the skin. Frequently the edema is very changeable in its manifestations; it comes and disappears at intervals with little evidence of a corresponding change in the urine or in such symptoms as blood pressure, anæmia, kidney function, etc.

There is no unanimity of opinion as to the way in which this type of edema is produced. Coincident with the diminished urinary flow, characteristic of acute glomerular nephritis, there is a retention of excretory substances such as urea, uric acid, sodium chloride, etc. When this occurs, it is obvious that the excessive fluid must be stored somewhere within the organism, and that a general retention of water in the tissue depots must follow. Recent studies on blood and plasma volume in renal edema indicate that this excessive fluid is not retained in the blood stream, but that the blood volume is kept decidedly constant despite the breakdown in the renal factor for fluid regulation. The excess of fluid is withdrawn to the various depots, that is, the soft tissues of the body, where latent fluid

of about six litres can be stored to become manifest clinically as edema only after this amount has been surpassed.

It is evident that edema is a protective mechanism, which prevents overloading of the vascular system, and it would appear further that this may be effected through the central fluid regulating center in some such manner as has been described previously under "Physiology of Fluid Regulation". The question arises: Does this explanation suffice for all the aspects of edema in acute glomerular nephritis? One writer (Elwyn[2]) believes so. However, in the recognition of a center for fluid regulation one must not lose sight of the possibility of local contributing causes. For instance, in the early edema of acute glomerular nephritis there is good evidence for the view that not only are the glomerular capillaries affected but that the capillaries throughout the body are involved similarly. Müller[27] and Wollheim and Moral[28] found irregularity, swelling, tortuosity and retardation of blood flow in the capillaries of the nail bed in acute nephritis. Moschcowitz[29], basing his conclusions upon the work of these and other observers remarks that "— the opinion is gaining ground that glomerular nephritis in reality represents a generalized disease of the capillaries, a capillaritis, in which the lesions of the glomerular capillaries are the most prominent manifestation". This view explains certain phases of edema on the basis of an increased permeability of capillaries and would help to account for the suddenness of the onset and the rather bizarre, localized distribution which cannot, at all times, be ascribed solely to the salt and water retention. This theory is further borne out by the work of Beckmann[30], who found the protein concentration of the edema fluids in acute glomerular nephritis higher than in any other form of edema. While the fluid in edematous tubular ne-

phritis (nephrosis) contained less than 0.1 per cent. protein, that in acute glomerular nephritis frequently showed over 1.0 per cent. Krogh[5] demonstrated that the normal capillary wall is impermeable to protein.

The course of the edema differs widely in various patients. To a great degree its progress, as mentioned previously, is independent of the other symptoms such as albuminuria. It may clear up altogether, leaving no demonstrable trace, in which case the edematous fluid is more or less rapidly eliminated by the kidneys; or it may continue as a symptom of subacute or chronic glomerular nephritis; it may disappear and return, apparently as the infectious agent responsible for the disease waxes or wanes in its activity.

Subacute Diffuse Glomerular Nephritis

This is a later stage of acute nephritis characterized by a crescent shaped proliferation of the cells of Bowman's capsule causing ultimate obliteration of the capillary tuft and eventual death of the patient from renal failure. Edema may or may not be present; it may be very marked or slight, and it may fluctuate a great deal. In other words, the accumulation of edematous fluid in the subcutaneous tissues and body cavities assumes the same characteristics as in the acute diffuse glomerular nephritis.

Chronic Diffuse Glomerular Nephritis

In considering the manifestations of edema in this form of Bright's disease a number of factors of distinct clinical importance must be considered.

1. The edema or anasarca may have exactly the same causes and clinical manifestations as those characteristic of the

acute type of the disease. Possibly the periods in which the retained fluid disappears completely or diminishes a great deal, either spontaneously or as the result of treatment, are more frequent and longer. This naturally would be expected in a chronic condition as compared with an acute one. It is especially noteworthy for the clinician that the amount of urine eliminated in the prone position is much greater than when the edematous patient is up and about. The simple procedure of complete rest in bed for a week or more often suffices to do away with a great deal of the retained fluid.

2. Because of the persistent elevation of blood pressure and the secondary anæmia usually present in chronic diffuse glomerular nephritis, the action of the heart may become inadequate and edema resulting from cardiac failure may occur. The use of digitalis in these cases often serves to hasten the elimination of the retained fluid. In some patients the part which the heart plays is determined easily; in others it is most difficult for the physician to be certain whether the myocardium is compensating or not. Even in the doubtful cases, digitalis may be effective. This finding has led us to resort to digitalis in the treatment of the edema of chronic diffuse glomerular nephritis almost as a routine measure. It may be that the digitalis is a diuretic, independent of its cardiac effect, and that this is at times responsible for the increased output of urine. However complicated this may be from the theoretical point of view, the practical fact remains that the digitalis often accomplishes a great deal and is not contraindicated in any way.

3. The secondary anæmia, so characteristic of advanced chronic nephritis, may result in edema of the dependent parts.

4. The edema accompanying the lowered albumin content of the blood may be found in this disease. This constitutes the nephrotic component in chronic diffuse glomerular nephritis. The characteristics of this element will be taken up under edematous tubular nephritis (genuine or lipoid nephrosis) a little further on. Edema produced in this way demands treatment entirely different from that accorded the fluid accumulations considered above.

5. As chronic diffuse glomerular nephritis progresses, it changes gradually into the pathological condition known as secondary contracted kidney. Among other lesions are those that occur in the glomeruli and the tubules. Many of the glomeruli are destroyed, but the remaining ones show considerable hypertrophy; each surviving glomerulus is thus capable of producing a great deal of urine, bringing about a glomerular polyuria. The remaining tubules show a wide lumen lined by a much flattened epithelium, which allows the urine to escape without the reabsorption of as much water as usual. The result of these conditions is that a large volume of urine with a low specific gravity is voided. The chronic nephritis, for these reasons, has changed from an oliguric to a polyuric state. The result is that the edema disappears, the subcutaneous tissues are no longer distended with fluid, and the skin becomes rather dry than otherwise. The kidneys no longer retain water but actually deprive the body of its fluid in their eagerness to have their remodelled secretory elements perform efficiently.

Focal Glomerular Nephritis

Focal glomerular nephritis is not accompanied by edema. This is one of the differential diagnostic points between this

and the diffuse type of glomerular nephritis, though it cannot be regarded as a sign of pathognomonic importance, since edema is often absent also in acute diffuse glomerular nephritis.

Edematous Tubular Nephritis

Tubular nephritis is the renal lesion that has come to be regarded as the one associated most commonly with a marked and persistent edema. As previously pointed out, there are very many cases where the kidney tubules are damaged without the concurrence of edema. This has prompted us (see chapter XI) to divide those forms of Bright's disease in which the tubules were primarily involved into albuminuric, edematous, anuric, and hypertensive and convulsive. This classification, according to diverse clinical signs and symptoms, indicates clearly that injury of the tubules does not entail a definite change in the extra-renal tissues. In other words, the edema occurring in *edematous tubular nephritis*, or *lipoid nephrosis*, or *chronic nephrosis*, as it is variously called, is brought on by processes among which the kidney plays only one part.

The edema appearing in edematous tubular nephritis is now believed to be the result of the diminished osmotic pressure of the blood colloids. The presence of a low albumin and normal, or raised, globulin content of the blood and its significance in regard to edema has been discussed earlier in this chapter and previously in chapter XI. Richard Bright made the original observation that the amount of protein in the blood was diminished in cases of albuminuria accompanied by edema. Epstein[31] in 1917 attributed a causal relation to the two conditions, and more recently his views have been verified by experimental evidence on animals. The experiments of Leiter[32] and of Barker and Kirk[19], in which the blood proteins of animals

were lowered while the red blood cells were maintained at a normal level, thus producing edema, have been mentioned. That such an edema is actually the result of a lowering of the blood proteins, especially of the albumin, and is not due to the kidney lesion is substantiated by the observation that edema accompanies inanition, as seen during the World War in the countries where the diet was markedly deficient in proteins and fats. Frisch, Mendel and Peters[33] confirmed the observations of A. Kohman[34] when they produced edema in white rats by means of continued low protein diets; the serum proteins in these animals were reduced distinctly. However, edema has been seen to disappear without change in concentration of plasma proteins. This McLean ascribes to compensating activity on the part of the fluid regulating center.

Thus the contentions of Epstein are substantiated completely, as to the concurrence of a diminished albumin content of the blood and edema, and their probable causal relationship in chronic nephrosis, edematous tubular nephritis or "diabetes albuminuricus", as Epstein chooses to name it. The reason for the lowered serum albumin appears to be the loss, in the urine, of this substance which is eliminated persistently in huge amounts in this disease. Whether this is due to the change in quality of the proteins and the effect of such a foreign material upon the glomerular capillaries, or to an increased permeability of the glomerular capillaries brought on by some other toxic agent, remains to be determined. That the capillary walls are more easily penetrated by large molecules, such as those of albumin, than under normal conditions, is established definitely (McLean[1]). It is apparent that in Bright's disease there are two distinct forms of edema, the one accompanying the acute and chronic diffuse forms of glomerular nephritis

and presumably due to a capillaritis, and the other associated with tubular nephritis and characterized by the diminution of serum albumin and the lowering of the albumin: globulin ratio in the blood, as shown in table 31.

In attempting to explain the *modus operandi* of the edema of nephrosis, a recent experiment of Richards[35] should not be overlooked. Following bichloride administration, Richards found by microscopic observation of living kidneys that the glomeruli showed no damage but were excreting at a much more rapid rate than normal; despite this, there was marked oliguria at the ureter, indicating some abnormal process within the course of the tubules. His explanation was that because of damage to the tubules they had lost their normal discriminatory reabsorptive power and were behaving like dead membranes, permitting the osmotic attraction of the blood in the surrounding capillaries to cause indiscriminate reabsorption of nearly all fluid and dissolved substances. The explanation generally accepted hitherto of the oliguria or anuria in bichloride of mercury poisoning is that plugged tubules are responsible for the suppression of urine.

Before leaving the subject of the edema accompanying tubular nephritis, the high cholesterol content of the blood, so frequently found in this condition, should be mentioned. It is well known that the cholesterol in the blood often rises to 1000 mg. per 100 c.c., or even higher, that is, to about five times the normal. No completely satisfactory explanation of this phenomenon has been given. The theory evolved by E. H. Fishberg[36] that this is a compensatory mechanism, as the total lipoids exercise a certain degree of osmotic pressure and thus supplant the loss of albumin from the blood serum, is interesting and worthy of consideration.

Vascular Nephritis

Edema does not occur in uncomplicated arterial or arteriolar lesions of the kidney. When edema is present in this type of nephritis, it is of cardiac origin, since hypertension, which often entails a myocardial insufficiency, is a frequent cause for, or an accompanying symptom of, vascular nephritis.

Composition of Edema Fluids

From the clinical aspect intricate analyses of subcutaneous, pleural and peritoneal fluids yield very little. Some of the simpler tests are of great help in differentiating transudates from exudates and in diagnosing the cause responsible for the exudates. Such procedures, although they are valuable diagnostic aids and easily carried out, are for some reason neglected in many laboratories. The significant routine clinical analyses of the edema fluids in Bright's disease will be enumerated here and subsequently some of the more detailed knowledge in regard to them will be taken up.

Routine Analysis of Pleural and Peritoneal Transudates in Bright's Disease

There are four determinations of distinct importance: inspection, specific gravity, the quantity of albumin and the differential leucocyte count of the sediment.

Inspection. — The fluids obtained from the pleural or abdominal spaces in Bright's disease usually are yellow in color and clear; at times they may be opalescent or chyliform in appearance due to the presence of fats or related substances. In exudates, excepting those of tuberculous origin, distinct turbidity is present; tuberculous exudates are clear and cannot

be differentiated from the transudates of Bright's disease on inspection. Bloody fluids are characteristic of malignant disease, especially if each succeeding tapping becomes more hemorrhagic; it is usually stated that tuberculous fluids may be markedly blood stained, but in my experience this has been very uncommon.

Specific gravity is one of the best means of differentiating transudates from exudates. The figures generally accepted as reliable guides are:

Specific gravity of a transudate of the pleura or peritoneum is below 1.015.

Specific gravity of an exudate of the pleura or peritoneum is above 1.017.

Protein content may be determined with sufficient accuracy for clinical, diagnostic purposes by means of the Esbach albuminometer. The fluid should be diluted so that the final reading is well within the marked scale on the tube.

Transudates of the pleura	contain less than	2.0% protein
Exudates of the pleura	contain more than	4.0% protein
Transudates of the peritoneum	contain less than	2.0% protein
Exudates of the peritoneum	contain more than	3.0% protein

Differential leucocyte count of the sediment reveals over ninety per cent. of small lymphocytes in all transudates; the same leucocytic picture is noted in tuberculous exudates of the pleura, though it is claimed that during the early stages, about the first two weeks, the polymorphonuclear cells may predominate. In all exudates and malignant diseases of the pleura and the peritoneum there is a larger number of polymorphonuclear cells.

Accurate chemical and physical analysis of the subcutaneous edemata fluid and of the pleural and peritoneal transudates

has yielded some interesting facts that are of considerable value in formulating the theories of edema. Some of these have been alluded to previously.

As long ago as 1850, C. Schmidt[37] contended that there was an unequal distribution of crystalloids and proteins between edemata fluids on the one hand and blood serum on the other. The explanation of this phenomenon is the constant fluctuation in the body's content of many of the crystalloids and the maintenance of an equal osmotic pressure between the edema fluids and the blood serum, regardless of the substances that are retained in either medium, to bring about stabilization of the fluid currents. The key to the matter is contained in the statement of Loeb, Atchley and Palmer[38]: "The relationships between blood serum and edema fluid seem to result from a simple membrane equilibrium influenced in part by the proteins present." These authors find the chloride content of edema fluid always higher than that of the serum; potassium on the other hand is exactly reversed; they find the sodium, carbonate, glucose, urea, calcium and freezing point about equal in the two fluids. Gollwitzer-Meier[39] on the other hand finds that calcium, sodium and carbonate are not absolutely balanced; she makes the very interesting observation that the composition of edema fluids is not constant, but that it varies according to whether the edema is increasing or diminishing. Of interest in this connection is the very significant observation of Denis and Minot[40] that the urea, uric acid and cholesterol content of edemata fluids may be influenced by the diet. The contention made by various authors that urea and other crystalloids are in about the same concentration in the pleural and peritoneal transudates and in the blood has, in my experience, not held true, and I have been unable to find anything

more than an approximate relation between them. It is universally agreed that fat and cholesterol are present in much smaller amounts in the edemata fluids than in the blood stream. The data of Beckman[30], showing that subcutaneous fluid in nephrosis contains 0.1 per cent. of albumin or less and in glomerular nephritis more than 1.0 per cent. already has been discussed.

The Treatment of Edema in Bright's Disease

In collaboration with S. Edward King

Methods of Observation

Routine observation of the edematous case of Bright's disease should include the measurement of the fluid intake and the proteins and calories of the diet, the volume of urine eliminated in 24 hours, the number, size and consistency of the bowel movements. The change in weight is the most reliable means of estimating the fluid balance of the body, since it is impossible to estimate accurately the total fluid intake including the considerable amount contained in the so-called solid foods, or to determine the quantity of water lost in the expired air, the stools or the perspiration. Examination of the progress of the subcutaneous edema, especially in the legs, genital region and back may give warning of impending danger of injury due to excessive distention. The heart action must be studied frequently to determine whether therapy focused upon the vascular system should be instituted. The abdominal and pleural cavities should be examined for accumulations of fluid. The blood urea nitrogen should be determined at intervals, and the findings used as a basis for the quantity of protein to be put into the diet or of urea to be administered as a diuretic.

The urinary specific gravity serves as a guide to the existing capacity of the body for water elimination, a specific gravity of 1.020 or over indicating that the renal excretion is defective in this respect, one of 1.010 or less showing that the maximal effectiveness of the renal tissue for fluid excretion is in force.

The treatment of edema should be *adjusted to the cause of the disorganized fluid balance.* The accumulation of fluid may be due to circulatory failure (cardiac edema), to toxic damage of the capillaries (the edema of diffuse glomerular nephritis), or it may be secondary to a diminished albumin content of the blood (the edema of edematous tubular nephritis, usually described as lipoid or genuine nephrosis). These various etiological factors demand individual consideration and will be taken up after the general anti-edemic measures, more or less applicable to all forms of fluid retention within the body, have been discussed.

Anti-edemic Measures

Rest in bed maintained throughout the 24 hours overcomes the effect of gravity; the more equal distribution of the edema fluid favors absorption from the tissues, and a diuresis often follows. When myocardial insufficiency exists, rest in bed is imperative from other points of view as well.

Limitation of fluid obviously is necessary. Thirst is intense in many cases with edema, but the impulse to drink copiously should be curbed. The fluid intake in severe cases of edema should not exceed 750 to 1500 c.c. daily; the actual amount allowed is to be governed, to a large extent, by the urinary output and body weight. The water eliminated by the skin, the lungs and the gastro-intestinal tract, although important, cannot be measured actually. The total fluid intake includes

the liquids ingested, the water contained in food and that formed through the oxidation of carbohydrates. Usually, the limitation of the liquid component of the diet suffices, but in severe cases the fluid present in food stuffs should enter into the calculations. For short periods of time, as in cardiac decompensation, the Karell diet, consisting of four glasses of milk (about 800 c.c.) and dry toast daily, is satisfactory. This diet is feasible for a few days only, and it becomes necessary to prescribe balanced, dry, low salt diets such as those of Keith, Smith and Whelan[41, 42]. These diets contain approximately 800 c.c. of water including that present in the solid as well as the liquid food; their mineral and vitamine contents are adequate. The basal diet contains 40 grams of protein and 1500 calories. The other diets are higher in protein, but fluid and salt are maintained at approximately the same level.

Sodium chloride restriction is of great importance in the control of edema. This was first noted by Widal and Javal[8] and Strauss[9] in 1902. Drastic restriction requires a calculated diet low in sodium. This is combined conveniently with a restricted fluid content in the diets of Keith, Smith and Whelan[41, 42], above mentioned. When weighed diets are not available the following diet list may be employed.

Salt-Poor Diet

Special Precautions: No salt, salt butter or milk is to be used in the preparation of the food nor added when eaten.

Breakfast:

Fruits: Fruits and fruit juices without restriction (citrous fruits, grapes and grape juice are recommended particularly because of high potassium content). Jams, jellies and marmalade.

Cereals: All cereals cooked without salt and served without milk or cream; omit all prepared cereals except those of known low salt content.

Eggs: In any form, prepared without salt, milk or cream.

Meat and Fish: All meats and fish permitted, if prepared by thorough boiling and broth containing the salt among other substances is discarded; *salted, dried and preserved meats and fish, meat extracts, meat puddings, sausages and bacon, stews, hash, meat and chicken pies, chipped beef, etc., must be avoided.*

Potatoes: In any form prepared without salt, milk, cream or cheese.

Bread Stuffs: Bread, cakes, biscuits, rusk, rolls and waffles prepared without salt.

Extras: Salt-free butter, honey, maple syrup, jams, jellies, marmalade, sugar.

Liquids: Coffee, tea, cocoa and chocolate; *milk not allowed.*

LUNCH, DINNER AND SUPPER:

Soups: Vegetable soups (prepared without milk, cream or meat stock) and purées without salt or salt butter but may be flavored with onion, savory herbs such as parsley, thyme and bay leaf. *Meat soups are not permitted.*

Meats and Fish: See breakfast.

Vegetables: All fresh vegetables permitted without addition of salt, salted butter, milk or cheese.

Fruits: All fresh or preserved fruits and jams or jellies.

Condiments: Pepper, mustard, oil, vinegar, garlic, onions and various savory herbs.

Desserts: Cakes, pies, pastry and puddings (if prepared without salt), tapioca, cornstarch.

Beverages: Coffee, tea, beer, ales, wines, grape juice, lemonade, orangeade, grapefruit juice. *Mineral waters are not allowed.*

FOODS NOT PERMITTED:

Table salt, salt butter, ordinarily prepared bread, cake, rolls and biscuits, prepared cereals, milk, butter milk, and all forms of prepared milks, cheese.

Salt water fish, sea foods, red meats (unless boiled and broth discarded).

All meat soups, dried and salted meats, sausages, meat puddings, meat extracts, preserved and salted fish as sardines, herrings, caviar, pickles and all obviously salted foods.

SPECIAL CONSIDERATION:

Exclusive of salted foods and table salt, added in preparation of food or when eaten, most of the salt in an ordinary diet enters through the medium of bread, salted butter and milk. If these are avoided or satisfactorily prepared, a salt-poor diet, adequate for all ordinary purposes may be obtained.

Fluids must be restricted in cases with edema. 600 c.c., about 3 glasses or cups of fluid, is the minimal amount that is feasible, and the quantity may have to be increased.

A high protein intake, when the urea nitrogen of the blood is at a level of 40 mg. per 100 c.c. or less, is very desirable in the treatment of edema. Such a diet is not injurious to the kidney (see treatment of chronic diffuse glomerular nephritis) and prevents the development of a secondary anæmia. By maintaining the albumin content of the blood serum at a normal level, a high protein diet checks the formation of edema (see first half of this chapter), it forestalls the advent of malnutrition and the attendant famine edema (Kriegsödem), and finally it acts as an excellent diuretic through the production of increased amounts of urea which are presented to the kidney for elimination.

Purgation is an aid in ridding the edematous patient of retained water. A considerable amount of fluid may be eliminated under the influence of magnesium sulphate, compound jalap powder and other cathartics or purges. Calomel and most other mercurial drugs we believe contraindicated because of the very real danger of producing a severe tubular nephritis and oliguria. Violent diarrhea is to be avoided, since it may be of more harm than benefit because of the discomfort, loss of sleep and physical depression it creates. Two, at the most three, loose movements a day are all that the patient should have.

Diaphoresis, induced by hot packs, hot air baths, electric light baths, pilocarpine, etc., is exhausting and may produce collapse in debilitated individuals. Although large amounts of fluid may be eliminated through the skin by these means, they do not, for some reason, serve to influence the edema ap-

preciably. Consequently, measures designed to promote loss of fluid through sweating largely have been discarded in the treatment of edema.

Aspiration or drainage of edematous fluid sometimes is forced upon the physician when the anasarca becomes extreme. *Tapping of the abdomen* usually is difficult and not very successful because of the very marked, often brawny, infiltration of the lower portion of the abdominal wall; peritonitis is a frequent occurrence after paracentesis in Bright's disease. Drainage of the lower extremities by means of Southey's tubes or multiple incisions is a form of treatment which is always mentioned but scarcely ever used. There is serious danger of a complicating erysipelas or cellulitis and, furthermore, although a good deal of fluid may be lost in this way, the relief afforded is not very great and scarcely ever of lasting value.

The removal of fluid from the pleural cavities by aspiration is by far the most effective of the mechanical means of treating the anasarca of Bright's disease; usually edema is extreme when hydrothorax is evident. The collection of fluid in the chest will embarrass the action of the heart and the lungs, and it may become necessary to remove it in order to prevent the suffocation of the patient in his own body fluids. In several of our cases thoracentesis has tided over a critical period, and, we believe, saved the life of markedly edematous individuals.

Diuretics

Diuretic drugs must be used with fine judgment. The idea that, because the amount of urine is small, the kidney should be stimulated has proved itself to be not only useless, but even harmful, in many cases of Bright's disease. There are a few simple facts that are worth remembering in this connection.

When edema is the result of *cardiac weakness*, preliminary digitalization and rest, combined with a low fluid and salt diet, often render it unnecessary to use diuretics at all. If they must be resorted to, they will be much more effective after such an initial period of treatment than without it. The purin group, especially theocin, frequently results in a remarkable increase in the urinary volume in this type of edema. The heart alone may be responsible for edema in Bright's disease — this is particularly true in hypertensive states — or it may be one of a number of factors that cause the edema. If myocardial insufficiency is either wholly or partly to blame for the edema, the above treatment should be instituted. Digitalis and rest may be ordered with confidence in all cases; the use of diuretics, however, has certain contraindications which will be mentioned below.

In *acute diffuse glomerular nephritis* and in *acute exacerbations of chronic diffuse glomerular nephritis* the use of diuretic drugs should be avoided, if possible. Such medications usually are without effect, while they may irritate the kidneys (particularly the mercury compounds) and thus be productive of an oliguria instead of an increase of the urinary flow. Finally, it is rare for the edema accompanying these forms of nephritis to require treatment, as the condition is a self-limited one and usually clears up spontaneously. There are occasional cases which are exceptions to the last statement, where the edema may persist for a long time and assume alarming proportions, but even under these circumstances diuretics are of doubtful value.

When a *marked degree of renal insufficiency* exists, as demonstrated by an elevation of the blood urea nitrogen to about 60 mg. per 100 c.c. or higher, diuretics should be avoided. Urea in itself is one of the most potent diuretics, and if the

kidney does not respond to it, it cannot be expected to answer to the stimulus of others, and, under the circumstances, they will tend to depress renal activity rather than to increase it.

Diuretics should, as a rule, be administered at intervals only. Karl Schlayer in 1912, then at Romberg's clinic in Tübingen, called my attention to this, and it has proved to be very good advice. Although a diuretic drug may have induced polyuria at first, its continuous use may result subsequently in oliguria because of "kidney fatigue". If there is no favorable response when a diuretic has been taken for one or, at the most, two days, this medication should be discontinued so that no distressing degree of kidney fatigue may result. If polyuria follows the administration of a diuretic, the drug may be repeated at three- or four-day intervals and usually will have the same favorable effect on repetition. Because of the intermissions, any possible depression of the kidney activity has been avoided. If the particular drug has not been effective, another may be substituted for it. Thus no harm can accrue to the patient, while we are finding the most efficacious medication and the one best suited to the particular case. The daily repeated dosage of certain diuretics, such as salyrgan, has been advocated recently; it remains to be determined whether the principle of intermittent administration is advisable for all diuretic medications, or whether there are exceptions to this rule.

(1) The *digitalis group* includes the standard preparations of digitalis, strophanthus and squill. The general indications, mode of action and methods of administration are detailed in the volume of this series on Diseases of the Heart[143]. The diuresis induced by these drugs is dependent upon increased efficiency of the general and renal circulation. Edema frequently develops in Bright's disease because of latent myocardial insufficiency which is not

manifested in the cardiac rate or rhythm nor by other signs or symptoms. It is a safe rule in all cases of edema to precede the use of other diuretics with at least tonic doses of digitalis (about 2 c.c. of a good tincture daily).

(2) The *purine* or *xanthine group* of diuretics are alkaloids, which cause vasodilatation of the smaller arteries of the body, particularly those of the heart and kidneys. Richards and Schmidt[43] observed that caffeine produced dilatation of the glomerular vessels in frogs, and increased the number of glomeruli with an active circulatory flow.

Caffeine, tri-methyl xanthine, is of limited value as a diuretic because of its pronounced cerebral action. Caffeine citrate and caffeine sodium benzoate in 0.3 to 0.5 gm. (5 to 7 grains) doses are used as cardiac stimulants.

Theobromine, although a weaker diuretic than caffeine by weight, has no undesirable cerebral action and may be employed in considerably larger doses without ill effects. A number of soluble double salts have been introduced such as the sodium salicylate or diuretin, sodium acetate or agurin, and calcium salicylate or theocalcin. None of these possess any advantages over the simple alkaloid. Taylor[44] reports that the dose of theobromine commonly recommended is not effective; only a slight diuresis was obtained with 2.6 gm. (40 grains) daily, but satisfactory urinary flow was produced by 5.2 gm. (80 grains). Marvin[45], and Grossman and Sander[46] emphasize the superiority of theobromine over its double salts although good therapeutic results may follow from giving 1.3 to 1.6 gm. (20 to 25 grains) of diuretin three times a day. Prolonged administration of theobromine and its derivatives brings about gastro-intestinal disturbances and the presence of red cells, albumin and casts in the urine.

Theophyllin, the natural alkaloid, or theocin, the synthetic product, is the most effective diuretic of the group. Because it is insoluble and irritating to the gastric mucosa, it is administered in capsules after meals in doses of 0.2 to 0.3 gm. (3 to 5 grains) for one and certainly not more than two days. Soluble theocin is a compound with sodium acetate, containing 60 per cent. of the alkaloid, which is tolerated better by the stomach, but apparently is less efficient. Euphyllin, later called metaphyllin, still more recently called thephylldin, a compound containing 78 per cent. of theophyllin combined with ethylenediamine, is more soluble, less irritating and said to be more active than the simple alkaloid. Comparative details regarding its diuretic activity are not conclusive, but euphyllin (or metaphyllin) is superior to all members of the group as a cardiac vasodilator[47].

A summary of the effect of the digitalis and the purine group of diuretics points to their successful application in the treatment of edema caused by myocardial insufficiency but not for the removal of accumulated fluid accompanying Bright's disease. Christian[48] epitomizes the situation in regard to these drugs when he says that in uncomplicated nephritis, where there is need for diuresis to remove edema, they do no good. In case myocardial weakness is a factor in the production of the edema, it is best either to digitalize the patient or resort to tonic doses of digitalis for a few days and then to employ a diuretic for a day, or possibly two, and repeat the medication after a three- or four-day interval. Of this group of diuretics, theocin, administered as 0.3 gm. (5 grains) in capsules three times a day is, by far, the most effective.

(3) *The saline diuretics:*

(*a*) The *neutral saline diuretics*, particularly potassium

chloride and potassium nitrate, have been suggested with the idea that they would replace sodium in the tissues and thus increase water excretion. Blum[49, 50] reported favorable results in cardiac and nephritic cases, and Adolph[51] confirmed this effect experimentally, but the frequency of toxic symptoms renders the use of these medications inadvisable.

(*b*) *Alkaline salts*, namely the acetates, citrates, and tartrates of potassium and ammonium, have long been employed as mild diuretics. They are frequently combined in diuretic mixtures such as Basham's, and Imperial drink. The citrates and acetates are non-toxic. Potassium acetate in 5 gram (75 grain) doses, and the citrate in doses from 30 to 50 grams ($7\frac{1}{2}$ to $12\frac{1}{2}$ drams) daily, have been used with good results by McCann[52].

The intravenous injection of hypertonic solutions of sodium carbonate and sodium chloride (Fischer's solution) may produce polyuria. Osman[53] has carried the use of the alkalies to the extreme of administering 75 grams of equal mixtures of sodium bicarbonate and potassium citrate daily over long periods. Although many of his results were excellent, several fatalities occurred as the result of an alkalosis in cases with poor kidney function. The general basis for this work is found in the earlier theories of Fischer[12]. Osman[53] cites some investigations by Hampson and Maisell on swelling of erythrocytes in various hydrogen ion concentrations to explain the anti-edemic action of both alkaline and acid salts. He believes that imbibition of fluid by the tissue colloids, which is increased in edema, is diminished under the influence of extreme acid and alkaline reactions.

It is unprofitable here to prolong this discussion in the field of colloid chemistry. The paradoxical action of alkalies and

acids in diminishing edema is best explained by Stieglitz[54]. He believes that this diuresis is brought about by the excretion of the excess acid or base in an effort to maintain the neutrality of the blood.

(*c*) *Acid salts* have been found to exert an active anti-edemic effect in all types of edema. They are compounds of strong acid radicles, chlorides, nitrates and sulphates with weak basic components such as ammonium, calcium and magnesium, which by hydrolysis in aqueous solution react as acids. Calcium salts were introduced first because of the effect of the calcium ion on capillary permeability as observed by Hamburger[55]. Blum[56], Hulse[57], Segal and White[58], Rockwood and Barrier[59], and Atchley, Loeb and Benedict[60] obtained diuretic effects with calcium salts in cases of nephritic edema, while Maase and Zondek[61] produced similar effects in cases of war edema. Calcium lactate was employed first in 15 gram doses, but calcium chloride subsequently was found to be superior in smaller doses. The latter salt is disagreeable in taste and may produce vomiting and diarrhea. Calcium nitrate in daily doses of 30 grams has been recommended by McCann[52], but this salt is potentially dangerous because of the possible formation of the toxic nitrite group. The mode of action of calcium salts in edema is now thought to be that of acid salts in general rather than a specific diuretic effect peculiar to calcium alone.

Ammonium salts, particularly ammonium chloride, are superior to calcium salts in that they are both more palatable and more effective. The dose of ammonium chloride or nitrate, usually recommended, is about 9 grams daily, which may be continued for a week or longer, until the desired effect is obtained. Jacobs and Keith[62], and Keith, Whelan and Bannick[63] report good diuretic effects with ammonium nitrate; while they

admit that toxic manifestations occur after the use of this drug, they believe them to be relatively unimportant. The danger of conversion of the nitrate radicle into the toxic nitrite makes caution in the use of this salt imperative. Magnesium chloride, magnesium sulphate and ammonium sulphate have been used also, but their value is limited because of undesirable cathartic action.

The investigations of Haldane[64], Gamble, Blackfan and Hamilton[65], Keith and Whelan[66], and Bannick and Keith[67] indicate that the diuretic action of the acid salts is due to the acidosis they produce. The ingestion of considerable quantities of these salts results in an increase of the acid radicles in the blood, notably the chlorides, with a corresponding fall in the plasma bicarbonate and pH. The excess of acid radicle is apparently corrected in several ways, by the excretion of an acid urine of about pH 5, but mostly by withdrawal of fixed base, namely sodium, from the tissues and its excretion in increased amounts in the urine. Secretion of urine is stimulated thereby to a marked degree. According to Keith and Whelan[66], free hydrochloric acid ingested in equivalent amounts also induces acidosis and diuresis. Following dilute acids and acid salts, Polland[68] noted an increase in the Addis urea ratio, indicative of an increase in renal efficiency, such as occurs with other known diuretics.

The acid salts should be employed with great caution in cases with diminished kidney function, since a severe degree of acidosis may develop when these salts are not excreted readily. The acid salts have been found to enhance the action of other diuretics; according to the advice of Keith and his co-workers, novasurol and salyrgan are preceded effectively by a course of ammonium chloride.

A summary of the value of the saline diuretics in Bright's disease indicates that the neutral and alkaline salts are not effective. The acid salts have produced good results; they are now largely used with the intention of bringing about a mild degree of acidosis that augments the action of novasurol or salyrgan. Ammonium chloride or ammonium nitrate, 8 to 12 grams a day, are the preferable acid salts. The salts are given the patient for two or three days, then the administration of salyrgan or novasurol is begun and the ammonium chloride or nitrate is continued.

(4) *The metallic diuretics:*

(*a*) *Inorganic mercury, as calomel*, was stressed in the treatment of edema by Jendrassik[69] in 1886. Mercury is a constituent of "Guy's pill" (containing a grain each of calomel, digitalis and squill) formerly widely used in the treatment of dropsy. The frequent sequel of stomatitis and tubular nephritis has brought this form of therapy into disrepute.

(*b*) *Novasurol or merbaphan*, a soluble organic mercurial compound, introduced by Ziegler[70] in 1917 for the treatment of syphilis, was discovered to possess remarkable diuretic properties by Saxl and Heilig[71]. This compound was found to be much less toxic than equivalent doses of inorganic mercury. Marked diuresis was reported to have resulted in cases of nephritis with edema by Keith and Whelan[72], Keith, Barrier and Whelan[73], and Howarth[74]; in hepatic ascites by Rowntree, and Keith and Barrier[75]; in pleurisy with effusion and in ascites due to malignancy or tuberculosis by Saxl and Heilig[76] and Kulcke[77]. The best effects, however, have been obtained in cardiac edema as reported by Crawford and McIntosh[78], Marvin[79] and Lambie[80].

There is a great difference of opinion as to the mode of

action of this diuretic. Nonnenbruch[81], Bohn[82], Tezner[83], and Saxl and Heilig[76] believe that novasurol acts largely upon the tissue and plasma colloids. Crawford and McIntosh[78], and Keith and Whelan[72] consider the effect to be upon both the tissues and the kidneys. Blum and Schwab[84] believe that its action is purely renal, as does Jackson[85], who notes changes in kidney volume and in the glomerular circulation following its use. Because the diuresis could be inhibited by atropin, Fodor[86] claimed its action was through a diuretic center in the mid-brain.

The effects produced by novasurol upon the blood are transient and confusing. Crawford and McIntosh[78] observed dilution of the blood, while Keith and Whelan[72] reported a slight concentration during the period of active diuresis. After intravenous administration diuresis usually begins within two hours and continues for from twelve to twenty-four hours, while after subcutaneous injection the effect is prolonged for forty-eight hours. Coincident with the augmented volume of urine, there is a marked increase in excretion of chlorides and total base. Novasurol is prepared as a neutral 10 per cent. aqueous solution, and the usual dose is from $\frac{1}{2}$ to 2 c.c. given at intervals of four to seven days. The average adult dose is 1 c.c. It is desirable to administer a preliminary dose of $\frac{1}{4}$ c.c. in all cases, so that signs of intolerance, i.e., severe salivation, diarrhea and hematuria, may be noted.

Toxic reactions with novasurol are common even following the use of small doses such as $\frac{1}{4}$ c.c. Headache, salivation, stomatitis, nausea, vomiting, diarrhea, purpuric eruptions, hematuria, albuminuria and icterus are the more usual sequelæ; uremia has developed in cases with poor renal function; fatalities have been reported by Redlich[87], Serby[88], Sprunt[89]

and Saxl[90]. Serby found evidence of both liver and renal irritation and therefore concluded that impaired renal or hepatic function are distinct contraindications to the use of novasurol. Johnstone and Keith[91], in an experimental study, produced tubular degeneration but noted that the toxicity of novasurol was considerably less than an equivalent amount of organic mercury. Tolerance varied in individual cases but could be increased by repeated small doses.

(*c*) *Salyrgan*, a mercury compound which is considerably less toxic than novasurol, has been introduced recently. This substance contains 36 per cent. mercury and is prepared in 1 c.c. ampoules of a 10 per cent. aqueous solution. The initial dose is ½ to 1 c.c., but doses up to 2½ c.c. may be given. Only the intramuscular or intravenous route is available since subcutaneous administration may produce severe local reactions.

The general indications are similar to those for novasurol. Brunn[92], Hersky[93], Gunzberg[94], Barker and O'Hare[95] and Agnew[96] observed neither general reactions nor evidence of renal irritation following several thousand injections. Gunzberg[94] pointed out that salyrgan could be tolerated at more frequent intervals than novasurol and employed it every other day. Agnew[96] noted the most marked effect within twelve hours after its administration and found that it continued, in many cases, for several days and in one case for nine days. The urinary changes are identical with those produced by novasurol and its action is similarly enhanced by the preliminary administration of acid salts.

(*d*) *Bismuth salts*, hypodermically administered, produce diuresis in cases of edema, according to Blum[97], Molnar[98] and Robitscheck[99]. These results were confirmed subsequently by Hanzlik et al[100, 101] who employed metallic bismuth suspended

in dextrose solutions, potassium bismuth tartrate and potassium bismuth salicylate in oil. The usual doses were 45 to 60 mgm. ($\frac{3}{4}$ to 1 grain) of the salts and 120 mgm. (2 grains) of metal, the former being more active. An increased urinary volume was noted within 12 to 16 hours following the injection, the diuresis becoming most marked after 48 hours and continuing for four days. The excretion of bismuth in the urine paralleled the increased urine volume. As the metal disappeared from the urine, the diuresis subsided. Albuminuria did not occur nor any depression in renal function, as evidenced by the phenol-sulphonaphthalein test. An increased urinary excretion of sodium chloride was noted by Blum[97]. No diuretic effect was obtained following oral administration of bismuth salts and, no traces of the metal appeared in the urine.

Summary of the Use of Metallic Diuretics in Bright's Disease. — The use of these drugs in our experience has not been very encouraging. The toxic effects incident to the administration of novasurol have led us to discard it entirely and resort to salyrgan, which, in our use of it, has proved satisfactory in this respect. We have had little experience with the bismuth preparations but have not been successful with them thus far. In the treatment of the edema of Bright's disease, the new mercurial salts have been very disappointing according to our observation; in cases of cardiac edema or ascites they have yielded occasional excellent results, even when other diuretics have failed. It is generally acknowledged that in many cases of nephritis no form of mercury should be employed, that is, in hemorrhagic nephritis, whether acute or chronic, and when there is marked impairment of renal function. This leaves only a limited number of edematous patients with Bright's disease in whom diuretics may be used, notably those with an

uncomplicated edematous tubular nephritis or lipoid nephrosis. The administration of salyrgan, to be sure, sometimes produces a temporary diuresis but no lasting freedom from the edema. As explained in the first half of this chapter, a permanent cure for these forms of edema must come through the elevation of the blood albumin. When temporary, symptomatic relief is desired, salyrgan, given intravenously or intramuscularly, 1 to 2½ c.c. every other day for several days, may be used. This medication is preceded for two or three days by a course of 8 to 12 grams of ammonium chloride or nitrate by mouth, the use of these acid salts being continued while the salyrgan injections are administered.

(5) *The endocrine diuretics:*

(*a*) *Thyroid* medication was recognized as a diuretic in chronic nephritis and cardiac disease by Percy[102] and later by Eppinger[21]. Epstein[22] has reported excellent results with very large doses of thyroid in edema accompanying tubular nephritis. Similar effects have been reported by others, but it is not generally conceded that thyroid is specific in this condition. This subject will receive detailed discussion below, under the caption "Treatment of Edema of Tubular Nephritis (Lipoid Nephrosis)".

(*b*) *Parathyroid.* Parathyroid has been introduced in the treatment of dropsy apparently with the belief that an increased blood calcium would influence the edema. The reports of Davidson[103], Mason[104], Meakins[105], McCann[106], Reitzel and Stone[107] and Lewis and Scriver[108] concerning the diuretic effect of parathyroid are inconclusive. In many cases parathyroid was combined with thyroid, while in others the diuresis appeared to be spontaneous.

In our personal experience, large doses of parathormone

(Collip) brought about no diuresis in cases of edema accompanying tubular nephritis or cardiac failure. The danger of producing hypercalcemia, which may result in death, necessarily will limit the utility of this drug even if any diuretic action is eventually established.

(6) *Crystalloid diuretics.* Among the crystalloids normally found in the body, glucose and urea have been resorted to as stimulants to renal activity. *Glucose* intravenously or by mouth often will result in a diuresis, and it has been used effectively by some physicians (John and Sherrill[109], Becher[110], Keith and Whelan[111] and Major[112]).

Urea as a diuretic was unconsciously pioneered by Morgagni who prescribed the urine of sheep in cases of edema. The first mention of urea as such, according to Achard[113], was made by Segalas and Vauquelin in 1822. Its value in reducing the fluid accumulations in the subcutaneous tissues and in the peritoneal and pleural spaces has been recognized by Volhard[114], Feilchenfeld[115], MacLean[116], Crawford and McIntosh[117] and King[118]. We believe it to be the diuretic of choice in all forms of edema except that following on passive congestion induced by myocardial insufficiency, when the combined effect of digitalis and theocine is preferable.

Urea is, contrary to traditional belief, not a toxic material. It is a matter of every day experience to find patients with a blood urea nitrogen of 100 mg. per 100 c.c. who are feeling perfectly well; a noted educator, pursuing an arduous life of lecturing entailing much travel, preparation of manuscripts and oratory, was found to have continuously a blood chemistry of this sort. The often cited observations of Hewlett, Gilbert and Wickett[119] that vertigo, headache, weakness and other symptoms were due to a rise in the blood urea are to be attributed to the

violent osmotic pressure variations of the blood when large amounts of urea are taken within too brief a period. In our experience, and that of others as well, when the urea in the blood becomes elevated (we have seen the urea nitrogen rise to 125 mg. per 100 c.c.) in the course of a few days, no further subjective or objective symptoms of any sort are manifested. We have never noted any harmful results, although we have resorted to urea as a diuretic very extensively, even in desperately ill patients.

Urea must be administered in large doses to be effective. The minimal effective dose is 10 grams three times a day, and this may be increased until 60 to 90 grams are taken in the 24 hours. The powdered urea is dissolved in coffee, tea, fruit juice or plain water and taken either before or after meals; it tastes much like epsom salts; most patients readily overcome any nausea the medication may cause and are content to continue with it when they appreciate what is being accomplished for them. Occasionally vomiting and diarrhea necessitate the discontinuance of the urea. It is very probable that the diuretic effect of high protein diets is, in part at least, due to the elevation of the blood urea which they produce.

The administration of urea must be guided by the level of the blood urea nitrogen. A moderate renal insufficiency, that is, one accompanied by a blood urea nitrogen level of 25 to 40 mg. per 100 c.c. is no contraindication to the use of the drug. Every four or five days, more or less according to the nature of the case, the blood urea should be determined and the blood urea nitrogen should not be allowed to exceed a level of 80 mg. per 100 c.c. A concentration above this point probably will not serve to augment the urinary flow. Urea should not be resorted to with patients whose kidney function is impaired to

such an extent that the blood urea nitrogen is 60 mg. per 100 c.c. or higher. In these cases, ingested urea accumulates rapidly in the blood without producing diuresis.

Clinical Application

There are three distinct types of edema occurring in Bright's disease as mentioned in the preceding pages. Each of them is the result of a different pathological physiological cause and consequently merits individual therapeutic consideration. More than one form of edema frequently is present in a case of Bright's disease. The varieties of edema are as follows:

1. Edema due to a generalized capillaritis, supposedly paralleling the changes in the renal glomeruli (nephritic edema).

2. Edema accompanying a lowered albumin content of the blood (nephrotic edema) (starvation edema) (hypo-albuminemic edema).

3. Edema secondary to myocardial insufficiency (cardiac edema).

The kinds of edema characteristic of the various forms of nephritis have been described previously in this chapter.

Treatment of the Edema Accompanying Acute Diffuse Glomerular Nephritis. — The presence of edema in this condition is not constant; in many instances there is no subcutaneous edema or accumulation of fluid in the body cavities. In prescribing therapy for this symptom it should be remembered in the first place that the fluid retention is associated with an inflammation of the blood vessels throughout the body, i.e., a generalized capillaritis, and further that in most cases the edema, and the acute nephritis as well, are self-limited. For both reasons the edema should be handled by a system of therapy that protects the kidneys and other tissues from all possible irritation and

thus encourages a rapid healing process. The measures mentioned under the treatment of acute diffuse glomerular nephritis in chapter XI, i.e., rest in bed, restriction as to water, salt and protein intake for a short period, followed by a more liberal food allowance when the very acute stage is over, usually suffice to control not only the inflammatory process in the kidney and other tissues, but the edema as well. The energetic administration of diuretics or other drugs or the use of physical therapy is contraindicated. In other words, the treatment at this stage is directed towards allaying the acute inflammatory reaction in the kidneys and other tissues, and no active steps should be taken to control the edema.

If moderate edema persists, no further measures than those required for the attempted control of the nephritis (that is, the renal lesions) may be necessary. On the other hand the fluid may collect in such quantities in the subcutaneous tissues and pleural and peritoneal cavities as to become a menace not only to the comfort but even to the life of the patient. When the daily weight increases, the urine is small in amount and of a high specific gravity, and there is an evident accumulation of serous transudates, more active treatment may be indicated.

Under these circumstances myocardial insufficiency, blood albumin depletion or anæmia may be important contributing factors to the edematous accumulation. Is it wise to resort to diuretics, and is the mechanical removal of fluid indicated? The results of the various forms of treatment should be watched very closely and modified according to indications.

Myocardial insufficiency occurs much more frequently in acute nephritis than is commonly supposed; the effects of hypertension, underfeeding, a preceding acute illness, the loss of blood and protein in the urine, the load of edematous fluid and

the presence of an infection all contribute either to burden the cardiac muscle or to damage it. In many instances tonic doses of digitalis have an excellent effect. About 2 c.c. (30 minims) of the tincture a day may be given for an indefinite time, possibly preceded by a double dose of the drug for two or three days.

If a diuresis is not effected within 4 or 5 days, and if the renal lesion, as revealed by the urinary sediment, is not active, theocin 0.2 to 0.3 gm. (three to five grains) three times a day for one day only, may be used. Judging by the results of the digitalis medication, myocardial weakness often exists in these patients even where no clear cut clinical signs point in this direction. The theocin may be repeated at intervals of three or four days, if the effect of the first dose is good; otherwise it should be discontinued entirely; the digitalis medication should be kept up for a longer period.

Depletion of the blood albumin (nephrotic component) or anæmia demand a high protein diet and possibly other forms of treatment that will be outlined in greater detail under the heading of edematous tubular nephritis later in this chapter. We do not believe that the feeding of large amounts of protein is harmful to the kidneys, even when red blood cells and considerable quantities of albumin are present in the urine. Because there is justification for a contrary opinion on this subject, we have not ordered such diets as routine in acute diffuse glomerular nephritis but have done so only when a persistent, marked edema or an anæmia developed. Besides raising the blood albumin the ingestion of a considerable amount of protein results in a rise of the blood urea which has a distinct diuretic effect. The diet should be as nearly salt-free as possible, and the fluids restricted; these and other principles have been

elaborated under the heading of anti-edemic measures in this chapter.

The use of diuretics to stimulate the activity of the kidneys during the course of an acute diffuse nephritis is generally condemned. The purine group are both ineffective and harmful in this condition (Christian[120]); when hematuria exists, recourse to the newer mercury-containing drugs, novasurol and salyrgan, is contraindicated. This leaves urea as the only diuretic substance which may be employed with some hope of success. The dosage, mode of administration, etc., of urea have been given and need not be repeated here.

Rarely when the anasarca becomes so marked as to threaten life, mechanical removal of the fluid must be performed. This is best accomplished by tapping the chest. Edema of the thighs and about the genital organs may cause a degree of distention that is well nigh intolerable; if possible, the use of incisions or Southey's tubes should be avoided, but at times they may prove necessary. Bland and White[121] recently have revived interest in the use of the tubes originally devised by Reginald Southey in 1877.

In conclusion we wish to emphasize the fact that the severe symptoms accompanying acute diffuse glomerular nephritis, including those due to edema, subside during the natural course of this renal disorder. Treatment, therefore, should be expectant and non-irritating as far as possible. The main exception to this course of events is the rare case which develops a subacute diffuse glomerular nephritis with its inevitably fatal termination; there is no form of treatment known at present, capable of preventing such an eventuality.

Treatment of the Edema of Subacute Diffuse Glomerular Nephritis. — The same principles of treatment apply to the edema accom-

panying this form of nephritis as to that of the acute type. In all the patients of this sort that we have seen, edema has not been a prominent symptom.

Treatment of the Edema of Chronic Diffuse Glomerular Nephritis. —When the edema is the accompanying symptom of an acute exacerbation of a chronic nephritis, the treatment is identical with that described for the acute diffuse glomerular form. When the disease is more or less stationery, that is, when the condition is chronic in character, the type of edema, which usually predominates, is that resulting from a diminished albumin content of the blood; this fact often is expressed by the term nephrotic component of chronic diffuse glomerular nephritis. It should not be forgotten that rest in bed often is sufficient to eliminate much of this edema. A diet low in fluid and as salt-free as possible should be insisted upon; in these and other respects the management of the case is identical with that detailed for the control of the edema in edematous tubular nephritis.

Many of these patients have a complicating hypertension and secondary anæmia, either or both of which may be partly responsible for the edema and merit special therapeutic consideration. Rest in bed, the regulation of diet and the use of digitalis and theocin, as described under acute diffuse glomerular nephritis, are indicated.

Many of these cases become edematous only at intervals, when they require rest in bed and intensive treatment; at other times they are up and about and following their pursuits happily and successfully in spite of a persistent albuminuria. Other patients never exhibit more than the slightest edema, and nearly all of them lose the tendency to water retention, when the kidney becomes sclerosed and the polyuria characteristic of the secondary contracted kidney begins. There are

instances however where the edema is marked and require constant attention to make even a bedridden existence possible.

The edema therapy in the chronic stage differs from that in the acute form of diffuse glomerular nephritis especially in one particular, that is, in the more liberal use of diuretics. Digitalis and purine derivatives are of value in augmenting the urinary flow only where there is cardiac insufficiency, but urea may be employed in both acute and chronic nephritis. The other diuretics not advisable in acute nephritis may be used here. The acid salts, ammonium nitrate or ammonium chloride, are the most effective, in 9 to 12 gram doses daily for two, three or more days and followed by salyrgan intramuscularly or intravenously every second day in 1 to 2 c.c. doses. When the acid salts are employed for long periods, frequent determinations of the alkali reserve of the blood are necessary to prevent acidosis, which may occur when renal function is impaired. When large and obstinate amounts of fluid accumulate, they may have to be removed by mechanical means. Aspiration of the chest is the best procedure; paracentesis abdominalis should be avoided whenever it is possible to do so; drainage of the lower extremities by means of Southey's tubes will relieve marked distention of the legs and genital region, but is attended with some risks as previously mentioned.

Treatment of the Edema in Edematous Tubular Nephritis (lipoid nephrosis, genuine nephrosis, diabetes albuminuricus). — The explanation of the genesis of the edema accompanying this form of nephritis has been given. Briefly it depends upon a lowering of the concentration of the blood albumin and a diminished colloid osmotic pressure of the blood. The edema, subjectively the most disturbing feature of this disease, is not secondary to the tubular lesions in the kidney.

The ideal therapy would be the removal of the etiological agent. This is a difficult matter to approach with any degree of confidence. The statement of Clausen[122] that infection of the paranasal sinuses by the staphylococcus is the cause of the symptom complex merits consideration; however, other forms of focal infection with different organisms, especially the pneumococcus, have been described by Stolz[123], Vandorfy[124], McElroy[125], Stewart[126] and Rosenberg[127]. The forms of therapy directed toward the remedying of the lowered blood albumin aim at the relief of a symptom and are not of fundamental value in the cause of this disease. Nevertheless, the feeding of adequate amounts of protein is a very great advance over the treatment of twenty-five years ago and has relieved much suffering that patients with Bright's disease formerly endured. The therapeutic procedures, usually resorted to for the elevation of the blood albumin content and the relief of edema in edematous tubular nephritis, require long continued effort on the part of physician and patient.

Although Linder, Lundsgaard and Van Slyke[128] found no quantitative relationship between the plasma proteins and variations in the edema, later observations by Mayrs[129], Cope[130] Moore and Van Slyke[131] and others indicate that the concentration of the plasma proteins and the resulting osmotic pressure of the blood are determining factors in non-cardiac edema. It has not been possible clinically to duplicate the experimental results of Barker and Kirk[19], that edema always appears when the blood albumin falls below one per cent. and disappears above this critical level. On the contrary, Wiener and Wiener[132] confirm the general experience that such extremely low albumin concentrations are rare, even in severe cases of edema. Probably other factors besides the osmotic pressure of the blood

proteins influence the edema in nephrosis. MacLean[116], Wordley[133] and King [118] consider that the immediate diuretic response to high protein diets is largely due to the urea in the circulation derived from the food proteins. The effect of the high protein diet often may be augmented by the use of urea, which has proved very satisfactory in this condition. The purine diuretics are ineffective. The acid salts, combined with salyrgan, have not as a rule brought about a diuresis comparable to that following urea.

Thyroid, originally used by Percy and later by Eppinger, was introduced by Epstein as a specific therapeutic agent in lipoid nephrosis. He drew an analogy between the disturbed metabolism of nephrosis and myxedema, considering the former a relative hypothyroidism. A very marked tolerance for thyroid is exhibited in this condition. In our experience 3.3 gm. (50 grains) of thyroid extract (0.065 gm. or a grain per pound of patient) may be taken by children for long periods without toxic reactions, and Epstein[134] reports using as much as 4 gm. (60 grains) of thyroid extract daily in adults, or 5 to 10 mg. of thyroxin intravenously at 5- to 10-day intervals. Small doses are used at the onset, and the dosage is increased progressively. The best results are obtained in conjunction with high protein diets, the thyroid aiding the utilization of protein, according to Epstein. The effect of thyroid apparently is non-specific, and negative results have been reported by Lewis and Scriver[108], Warfield[135], Major[136] and Shih-Hao[137]. In other cases, the improvement with thyroid therapy is only temporary, since marked edema may develop during the course of treatment.

Very large doses of thyroid are necessary if the removal of the edema is to be effected. This medication should be used until signs of hyperthyroidism become evident, when it must be

curtailed or stopped for the time being, to be resumed when the edema reappears. Patients whose blood cholesterol is at a high level often tolerate large doses of thyroid but become sensitive to it when the blood cholesterol diminishes. This interrelationship between the cholesterol in the blood and thyroid medication has been noted by Epstein, and we have found it to hold true in some of our patients.

Epstein[134] observed the rapid disappearance of edema in some cases of nephrosis during the course of an intercurrent infection and ascribed it to the metabolic stimulation of the infection and increase in body temperature. Upon this basis the use of non-specific protein therapy has been tried, and Major[136] reports considerable improvement in some cases following the use of typhoid vaccine.

Edematous tubular nephritis, particularly in children, very frequently is associated with some demonstrable suppurative focus of infection. This focus generally is situated in the upper respiratory tract, the nasal accessory sinuses, middle ear, mastoid cells or tonsils. The occurrence of this syndrome in tuberculosis, emphasized by Landouzy and Bernard[138], is not at all uncommon in our personal experience. René[109] found this condition in a large proportion of advanced cases of phthisis, while Simon[140] reports an incidence of over 6 per cent. in a considerable number of cases with bone and joint tuberculosis. It may develop in the course of chronic infections and with malignancy. In cases of prolonged suppuration, septic or tuberculous, amyloidosis may complicate the picture and alter the prognosis. A number of cases have been described by Munk[141] associated with syphilis, especially during the secondary stage. Irradication of the suppurative focus, when possible, is desirable, but when advanced pulmonary disease or malignancy

is present, this is impossible. In cases associated with syphil vigorous anti-luetic therapy is indicated, regardless of t renal pathology.

The edema of this condition usually is very persistent, ar if it does disappear, it is very prone to return. There a occasional cured cases on record in which not only the ede but also the albuminuria has ceased. Epstein[22] has reported number of such results, and we have had several. Since t dropsy is likely to be of long duration, and because of t chronic and recurrent character of the edema, none of the ste and procedures detailed above under routine observation an in the section on anti-edemic measures, should be omitted. mechanical removal of fluid becomes necessary, the suscept bility of these patients to infection should be taken into accoun The peritoneal cavity especially is subject to invasion by th pneumococcus or streptococcus. An apparently spontaneou peritonitis is frequent. It is remarkable how frequently thes patients recover from such an event; on the other hand, th inflammation is likely to return, and any one of these attack may prove fatal.

Many of the signs and symptoms of edematous tubula nephritis may be attributed to inanition, the lowered albumi content of the blood plasma, the edema, the high blood choles terol, the anatomical and functional changes in the thyroid gland, noted by Wolbach and Blackfan[142], and in other tissues. It is probable that not only the blood and the thyroid, but that all muscular and glandular tissues as well have become depleted. There is no better way in which to remedy such a tissue affection than by a high protein, high caloric diet. It is well known that the starved person can assimilate very readily enormous amounts of protein. The same is true of the patient with

chronic Bright's disease. The availability of protein foods has been discussed extensively above under the treatment of chronic diffuse glomerular nephritis in chapter XI, and reference is made to that section of the book for any moot points in regard to this controversial subject. A high protein, high caloric diet is urgently indicated in edematous tubular nephritis, not only as an aid in treating edema, but also to prevent and remedy devitalization of body tissues, entailed by a prolonged albuminuria.

A word of caution should be added in regard to the management of edema in lipoid nephrosis. The treatment, just outlined, covers the problems encountered in regulating one form of edema; however, in tubular nephritis there may be other causes for fluid accumulation in addition to those of the typical edema. The physician must be constantly on his guard to detect myocardial insufficiency or a generalized capillaritis or both in his patient with edematous tubular nephritis, and give these due attention.

The Treatment of the Edema in Vascular Nephritis. — A marked elevation of blood pressure is often the cause for the development of arteriosclerosis in the kidney. This hypertension may result also in cardiac hypertrophy and dilatation and subsequently in myocardial failure. The latter is responsible for the edema typical of arterial nephritis or nephrosclerosis. The edema of this form of nephritis is, therefore, purely of cardiac origin and should be accorded the same treatment as that accompanying any case of cardiac decompensation, modified to meet the degree of renal impairment the sclerosis of the kidneys may impose. The treatment for this type of edema has been outlined under the heading of treatment of the edema of chronic diffuse glomerular nephritis. For full details the volume of this series on diseases of the heart[143] may be consulted.

Bibliography

1. McLean, F. C.: Edema as a problem in physiological regulation, Physiolog. Rev., **5**: 618, 1925.
2. Elwyn, H.: Edema and Its Treatment, The Macmillan Co., New York, 1929.
3. Kylin, E.: Die Hypertoniekrankheiten, Berlin, 1926.
4. Donnan, F. G.: Theorie der Membrangleichgewichte und Membranepotentials bei Vorhandensein von nicht dialysierenden Elektrolyten. Ein Beitrag zur Physikalisch-chemischen Physiologie, Zeitsch. f. Elektrochemie, **17**: 572, 1911.
5. Krogh, A.: The Anatomy and Physiology of the Capillaries, New Haven Press, New Haven, 1922.
6. Landis, E. M.: Micro-injection studies of capillary permeability, Am. Jour. Physiol., **83**: 528, 1928.
7. Freund, H.: Die treibenden Kräfte für den Flüssigkeitsstrom im Organismus, Arch. f. exp. Path. u. Pharm., **95**: 206, 1922.
8. Widal, F. and Javal, A.: La chloruremie et la cure de dechloruration, Jour. de Physiol. et de Path. gen., **5**: 1123, 1903.
9. Strauss, H.: Die chronischen Nierenentzündungen, A. Hirschwald, Berlin, 1902.
10. Fishberg, A. M.: Hypertension and Nephritis, Lea and Febiger, Philadelphia, 1930.
11. Cantarow, A. and Gordon, B.: The effect of parathyroid on certain factors underlying the production of edema. Arch. Int. Med., **42**: 939, 1928.
12. Fischer, M. H.: Œdema and Nephritis, ed. 3., John Wiley and Sons, New York, 1921.
13. Loeb, L.: Edema, Medicine, **2**: 171, 1923.
14. Hülse, W.: Untersuchungen über Inanitionsödeme. Ein Beitrag zur Pathologie des Odems, Virchow's Arch. f. path. Anat., **225**: 234, 1918.
15. Starling, E. H.: On the absorption of fluids from the connective tissue spaces, Jour. Physiol., **19**: 312, 1896.
16. Fishberg, E. H.: Relation between colloid osmotic pressure and concentration of serum proteins, Proc. Soc. Exp. Biol. and Med., **26**: 1, 1928.
17. Cohn, E. J., Hendry, J. L. and Prentiss, A. M.: Studies in physical chemistry of proteins, Jour. Biol. Chem., **63**: 721, 1925.
18. Leiter, L. and McLean, F. C.: Experimental edema, Jour. Clin. Invest., **7**: 493, 1929.

19. Barker, M. H. and Kirk, E. J.: Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, Arch. Int. Med., **45**: 319, 1930.
20. Marx, H.: Untersuchungen über dem Wasserhaushalt. (II Mitteilung.) Die psychische Beeinflussung des Wasserhaushaltes, Klin. Wchnschr., **5**: 92, 1926.
21. Eppinger, H.: Zur Pathologie und Therapie des menschlichen Oedems., Berlin, 1917.
22. Epstein, A. A.: Thyroid therapy and thyroid tolerance in chronic nephrosis, Jour. Am. Med. Assoc., **87**: 913, 1926.
23. Aub, J. C.: Calcium and phosphorus metabolism. Harvey Lectures, 1928–1929, 151, Williams and Wilkins Co., 1930, Baltimore.
24. Myers, W. A.: Obstructive anuria, Jour. Am. Med. Assoc., **85**: 10, 1925.
25. Brown, G. E. and Rowntree, L. G.: Blood volume in edema of glomerular nephritis and nephrosis, Arch. Int. Med., **41**: 44, 1928.
26. Cohnheim, J. and Lichtheim, L.: Über Hydrämie und hydrämisches Oedem, Virchow's Arch. f. path. Anat., **69**: 106, 1877.
27. Müller, Otfried: Die Kappillaren der menschlichen Oberfläche, Stuttgart, 1922.
28. Wollheim, E. and Moral, H.: Kapillarmikroskopische Untersuchungen über die Temperaturreaktionen der peripheren Gefässe, Med. Klin., **22**: 1999, 1926.
29. Moschcowitz, E.: Cause of hypertension of the greater circulation, Jour. Am. Med. Assoc., **93**: 347, 1929.
30. Beckman, K.: Odemstudien, Deutsch. Arch. f. Klin. Med., **135**: 39, 1921.
31. Epstein, A. A.: Concerning the causation of edema in chronic parenchymatous nephritis: method for its alleviation, Am. Jour. Med. Sc., **154**: 638, 1917.
32. Leiter, L.: Experimental edema, Proc. Soc. Exper. Biol. and Med., **26**: 173, 1928.
33. Frisch, R. A., Mendel, L. B. and Peters, J. P.: The Production of edema and serum protein deficiency in white rats by low protein diets, Jour. Biol. Chem., **84**: 167, 1930.
34. Kohman, E. A.: Experimental production of edema as related to protein deficiency, Am. Jour. Physiol., **51**: 378, 1920.
35. Richards, A. N.: Methods and Results of Direct Investigations of the Function of the Kidney, Baltimore, 1929.
36. Fishberg, E. H.: Relations of serum proteins and lipoids to osmotic pressure, Jour. Biol. Chem., **81**: 205, 1929.

37. Schmidt, C.: Charakteristik d. Epidemischen Cholera, Leipzig, 1850.
38. Loeb, R. F., Atchley, D. W. and Palmer, W. W.: On the equilibrium condition between blood serum and serous cavity fluids, Jour. Gen. Physiol., **4**: 591, 1922.
39. Gollwitzger-Meier, K.: Zur Ödempathogenese, Ztschr. f. d. ges. exper. Med., **46**: 15, 1925.
40. Denis, W. and Minot, A. S.: The nonprotein constituents of edema fluids, Arch. Int. Med., **20**: 879, 1917.
41. Keith, N. M., Smith, F. H. and Whelan, M.: The therapeutic use of diets low in water and in mineral content, Arch. Int. Med., **37**: 550, 1926.
42. Keith, N. M., Smith, F. H. and Whelan, M.: The therapeutic use of diets low in water and in mineral content, Jour. Am. Dietet., **2**: 233, 1926.
43. Richards, A. N. and Schmidt, C. F.: Description of glomerular circulation in frog's kidney, Jour. Physiol., **71**: 178, 1924.
44. Taylor, L.: Clinical studies in caffein, Arch. Int. Med., **14**: 769, 1914.
45. Marvin, H. M.: Value of xanthine diuretics in congestive heart failure, Jour. Am. Med. Assoc., **87**: 2403, 1926.
46. Grossman, M. and Sander, J.: Zur klinischen Pharmakologie der Diuretika, Wien. klin. Wchnschr., **38**: 405, 1925.
47. Smith, F. M., Miller, G. H. and Graber, V. C.: The effect of caffein sodio-benzoate, theobromin sodio-salicylate, theophyllin and euphyllin on the coronary flow and cardiac action of the rabbit, Jour. Clin. Invest., **2**: 157, 1925.
48. Christian, H. A.: Diuretics in the treatment of cardio-vascular and renal disease, Jour. Indiana Med. Assoc., **20**: 422, 1927.
49. Blum, L., Aubel, E. and Levy, R.: L'action diurétique des sels de potassium dans les épanchements ascitiques et dans les oedemes, Bull. de la Soc. médicale des Hopitaux, Paris, **45**: 1504, 1921.
50. Blum, L., Aubel, E. and Hausknecht, R.: Le mecanisme de l'action du chlorure de sodium et du chlorure de potassium dans les nephrites hydropigenes, Compt. rend. Soc. de Biol., **85**: 123, 1921.
51. Adolph, E. F.: Excretion of water by the kidneys, Am. Jour. Physiol., **65**: 419, 1923.
52. McCann, W. S.: The management of dropsies, New York State Jour. Med., **28**: 1395, 1928.
53. Osman, A. A.: The use of alkalis in the treatment of Bright's disease, and their prophylactic value in this and other conditions associated with impairment of renal function, Guys Hosp. Rep., **77**: 386, 1927.

54. Stieglitz, E. J.: Alkalis and renal injury, Arch. Int. Med., **41**: 10, 1928.

55. Hamburger, R. J.: Über die Bedeutung der Kalium und Calciumionen für das künstliche Ödem und für die Gefässweite, Biochem. Ztschr., **128**: 153, 1922.

56. Blum, L., Aubel, E. and Hausknecht, R.: Action diurétique des sels de calcium; mecanisme de cette action, Compt. rend. Soc. de Biol., **85**: 950, 1921.

57. Hülse, W.: Über den Einfluss der Kalksalze auf Hydrops und Nephritis, Zentralbl. f. inn. Med., **41**: 441, 1920.

58. Segal, H. N. and White, P. D.: Clinical observations on the value of calcium chloride as a diuretic and its influence upon the circulatory mechanism, Am. Jour. Med. Sc., **170**: 647, 1925.

59. Rockwood, R. and Barrier, C. W.: Calcium treatment for edema, Arch. Int. Med., **33**: 643, 1924.

60. Atchley, B. W., Loeb, R. F. and Benedict, E. M.: Physiochemical studies of calcium chloride diuresis, Jour. Am. Med. Assoc., **80**: 1643, 1923.

61. Maase, C. and Zondek, H.: Das Kriegsödem, Berl. klin. Wchnschr., **54**: 861, 1917.

62. Jacobs, M. F. and Keith, N. M.: The use of diuretics in cardiac edema, Med. Clin. North America, **10**: 605, 1926.

63. Keith, N. M., Whelan, M. and Bannick, E. G.: The action and excretion of nitrates, Arch. Int. Med., **46**: 797, 1930.

64. Haldane, J. B. S.: Experiments on the regulation of the blood's alkalinity, Jour. Physiol., **55**: 265, 1921.

65. Gamble, N. L., Blackfan, K. D. and Hamilton, B.: A study of the diuretic action of acid producing salts, Jour. Clin. Invest., **1**: 359, 1925.

66. Keith, N. M. and Whelan, M.: A study of the action of ammonium chloride and organic mercury compounds, Jour. Clin. Invest., **3**: 149, 1926.

67. Bannick, E. G. and Keith, N. M.: The treatment of nephritis and nephrosis with edema, Jour. Am. Med. Assoc., **91**: 1944, 1928.

68. Polland, W. S.: Effects of diuretics upon urea excreting capacity of the kidney, measured by Addis' ratio, Am. Jour. Physiol., **85**: 141, 1928.

69. Jendrassik, E.: Das Calomel als Diureticum, Deutsch. Arch. f. klin. Med., **38**: 499, 1885.

70. Zeigler, K.: Novasurol ein neues Quicksilbersaltz sur Syphilisbehandlung, München. med. Wchnschr., **64**: 1257, 1917.

71. Saxl, P. and Heilig, R.: Ueber die diuretische Wirkung von Novasurol und anderen Quicksilberinjektionen, Wien. klin. Wchnschr., **33**: 943, 1920.
72. Keith, N. M. and Whelan, M.: The effect of novasurol on the composition of blood and urine, Am. Jour. Physiol., **72**: 195, 1925.
73. Keith, N. M., Barrier, C. W. and Whelan, M.: Diuretic action of ammonium chloride and novasurol in cases of nephritis with edema, Jour. Am. Med. Assoc., **85**: 799, 1925.
74. Howarth, R.: Novasurol and other diuretics in cardiac œdema, Brit. Med. Jour., **1**: 186, 1926.
75. Rowntree, L. G., Keith, N. M. and Barrier, C. W.: Novasurol in the treatment of ascites in hepatic disease, Jour. Am. Med. Assoc., **85**: 1187, 1925.
76. Saxl, P. and Heilig, R.: Ueber die Novasuroldiurese, Ztschr. f. d. ges. exper. Med., **38**: 94, 1923.
77. Kulcke, E.: Novasurol als Diureticum, Klin. Wchnschr., **1**: 622, 1922.
78. Crawford, J. H. and McIntosh, J. F.: The use of novasurol in cardiac edema, Jour. Clin. Invest., **1**: 333, 1925.
79. Marvin, H. M.: Merbaphen (novasurol) as a diuretic in congestive heart failure, Jour. Am. Med. Assoc., **87**: 1016, 1926.
80. Lambie, C. G.: Novasurol and other diuretics in cardiac œdema, Brit. Med. Jour., **1**: 80, 1926.
81. Nonnenbruch, W.: Ueber die Wirkung des Novasurols auf Blut und Diurese, München. med. Wchnschr., **68**: 1282, 1921.
82. Bohn, H.: Experimentelle Studien uber die diuretische Wirkung des Novasurals, Klin. Wchnschr., **2**: 352, 1923.
83. Tezner, O.: Zum Mechanismus der Novasurolwirkung, Med. Klin., **19**: 788, 1923.
84. Blum, L. and Schwab, H.: L'action diurétique des composes mercuriels, Press méd., **30**: 1081, 1922.
85. Jackson, D. E.: The pharmacological action of mercury in organic combination, Jour. Pharm. & Exper. Therap., **29**: 471, 1926.
86. Fodor, E.: Ueber das Indikationsgebiete des Novasurols als Diuretikum, Med. Klin., **19**: 684, 1923.
87. Redlich, F.: Letale Quicksilberintoxikation nach einmaliger Novasurolinjektion, Wien. klin. Wchnschr., **38**: 350, 1925.
88. Serby, A. M.: The pharmacology and therapeutics of novasurol, Arch. Int. Med., **38**: 374, 1926.
89. Sprunt, D. H.: Renal damage following administration of merbaphen (novasurol), Arch. Int. Med., **46**: 494, 1930.

90. Saxl, P.: Letale Quicksilberintoxikation nach einmaliger Novasurolinjection, Wien. klin. Wchnschr., **38**: 437, 1925.
91. Johnstone, B. I. and Keith, H. M.: Toxicity of novasurol (merbaphen); its action on kidney of rabbit, Arch. Int. Med., **42**: 189, 1928.
92. Brunn, F.: Salyrgan, ein neues injizierbares Diuretikum, Wien. klin. Wchnschr., **37**: 901, 1924.
93. Hersky, P.: Erfahrungen mit Salyrgan, München. med. Wchnschr., **721**: 515, 1925.
94. Gunzberg, M.: Klinische Erfahrungen über Salyrgan, ein neuse Diuretikum, Deutsche med. Wchnschr., **51**: 604, 1925.
95. Barker, M. H. and O'Hare, J. P.: The use of salyrgan in edema, Jour. Am. Med. Assoc., **91**: 2060, 1928.
96. Agnew, G. H.: Salyrgan as a diuretic, Canad. Med. Assoc. Jour., **18**: 45, 1928.
97. Blum, L.: L'action diurétique du bismuth; mécanisme de cette action, Compt. rend. Soc. de biol., **88**: 461, 1923.
98. Molnar, A. L.: Uber die Diuretische Wirkung der Wismutsalze, Klin. Wchnschr., **4**: 1287, 1925.
99. Robitschek, W.: Uber die Diuretische Wirkung der Wismutsalze, Med. Klin., **22**: 1026, 1926.
100. Mehrtens, H. G. and Hanzlik, P. J., Marshall, D. C. and Brown, W. S.: Bismuth as a diuretic, Jour. Am. Med. Assoc., **91**: 223, 1928.
101. Hanzlik, P. J., Bloomfield, A. L., Stockton, A. B. and Wood, D. A.: Diuresis from water soluble bismuth, Jour. Am. Med. Assoc., **92**: 1413, 1929.
102. Percy, J. F.: Thyroid extract in nephritis, Jour. Am. Med. Assoc., **59**: 1708, 1912.
103. Davidson, J. R.: A case of adolescent myxedema, accompanied by tetany of parathyroid origin, treated with Collip's parathyroid extract, Canad. Med. Assoc. Jour., **15**: 803, 1925.
104. Mason, E. H.: A case of chronic nephritis treated with Collip's parathyroid extract, Canad. Med. Assoc. Jour., **16**: 538, 1926.
105. Meakins, J. C.: The reaction of chronic nephrosis to thyroid and parathyroid medication, Jour. Am. Med. Assoc., **89**: 149, 1927.
106. McCann, W. S.: Diuretic action of parathyroid extract (Collip) in certain edematous patients, Jour. Am. Med. Assoc., **90**: 249, 1928.
107. Reitzel, R. J. and Stone, C. T.: Parathyroid extract (Collip) as a diuretic, Jour. Am. Med. Assoc., **91**: 1288, 1928.
108. Lewis, D. S. and Scriver, W. de M.: The response of chronic ne-

phrosis to parathyroid and thyroid medication, Ann. Int. Med., **2**: 66, 1928.

109. John, H. J. and Sherrill, J. W.: Influence of glucose ingestion on diuresis, Jour. Metab. Research, **1**: 109, 1922.

110. Becher, E.: Studieren über die Diurese durch hypertonische Lösungen von Salzen, Harnstoff, Harnstoffderivaten und Zukern, ein Beitrag zur Kenntnis des Vorganges der Harnbereitung, München. med. Wchnschr., **71**: 499, 1924.

111. Keith, N. M. and Whelan, M.: Changes in body temperature and metabolism accompanying experimental marked diuresis, Am. Jour. Physiol., **77**: 688, 1927.

112. Major, R. H.: Diuretics, Jour. Kansas Med. Soc., **27**: 163, 1927.

113. Achard, C. H.: The Œdema of Bright's Disease, Macmillan Co., New York, 1930.

114. Volhard, F.: Die doppelseitigen haematogenen Nierenkrankheiten, Berlin, 1918.

115. Feilchenfeld, J.: Ueber Harnstoff als Diureticum, Therap. d. Gegenw., **21**: 273, 1919.

116. MacLean, H.: Modern Methods in the Diagnosis and Treatment of Renal Disease, 1924.

117. Crawford, J. H. and McIntosh, J. F.: The use of urea as a diuretic in advanced heart failure, Arch. Int. Med., **36**: 530, 1925.

118. King, S. E.: The diuretic action of urea and high protein diets, Med. Clin. North America, **10**: 963, 1927.

119. Hewlett, A. W., Gilbert, Q. O. and Wickett, A. D.: The toxic effects of urea on normal individuals, Arch. Int. Med., **18**: 636, 1916.

120. Christian, H. A. and O'Hare, J.: Nephritis, The Oxford Med., Oxford Univ. Press, **3**: 685, New York, 1930.

121. Bland, E. F. and White, P. D.: The Use of mechanical measures in the treatment of obstinate edema, Jour. Am. Med. Assoc., **95**: 1489, 1930.

122. Clausen, S. W.: Parenchymatous nephritis; infection of paranasal sinuses as etiology, Am. Jour. Dis. Child., **29**: 587, 1925.

123. Stolz, E.: Ueber die sogennante Pneumokokkennephrose, Med. Klin., **18**: 1376, 1922.

124. Vandorfy, J.: Ein mit Pneumococcus Peritonitis verlaufender Fall von Nephrose, Med. Klin., **17**: 657, 1921.

125. McElroy, J. B.: Nephrosis, Jour. Am. Med. Assoc., **89**: 940, 1927.

126. Stewart, W. B.: The pneumococcus in nephrosis, Jour. Med. Soc., New Jersey, 1930.

127. Rosenberg, M.: Die klinik der Nierenkrankheiten, Kurs Vorlesungen für Praktische Arzte und Studierende, Berlin, 1927.
128. Linder, G. C., Lundsgaard, C. and Van Slyke, D. D.: The concentration of the plasma proteins in nephritis, Jour. Exper. Med., **39**: 887, 1924.
129. Mayrs, E. B.: The functional pathology of nephritis, Quart. Jour. Med., **19**: 273, 1926.
130. Cope, C. L.: The osmotic pressure of the blood proteins in nephritis, Quart. Jour. Med., **22**: 91, 1928.
131. Moore, N. S. and Van Slyke, D. D.: The relationship between the plasma gravity, the plasma protein concentration and edema in nephritis, Jour. Clin. Invest., **8**: 337, 1930.
132. Wiener, H. J. and Wiener, R. E.: Plasma proteins, Arch. Int. Med., **46**: 236, 1930.
133. Wordley, E.: The effect of high protein diet in nephritis, Quart. Jour. Med., **14**: 88, 1920.
134. Epstein, A. A.: Diabetes albuminuricus or chronic nephrosis, New York State Jour. Med., **28**: 1335, 1928.
135. Warfield, L. M. and Murphy, F. D.: Lipoid nephrosis, Trans. Assoc. Am. Physicians, **41**: 82, 1926.
136. Major, R. H.: Chronic nephrosis, is it a clinical entity? West Virginia Med. Jour., **25**: 449, 1929.
137. Shih-Hao, L.: The effect of thyroid medication in nephrosis, Arch. Int. Med., **40**: 72, 1927.
138. Landouzy, L. and Bernard, L.: La néphrite parenchymateuse chronique (des tuberculeux), Presse méd., **9**: 121, 1901.
139. René, J. A.: Nephritis in far advanced pulmonary tuberculosis, U. S. Vet. Bur. Med. Bull., **4**: 535, 1928.
140. Simon, S.: Zur Klinik der Nephrose bei Knochen und Gelenktuberculose, Deutsch. Arch. f. klin. Med., **163**: 87, 1929.
141. Munk, F.: Die Nephrosen, Med. Klin., **12**: 1019, 1916.
142. Wolbach, S. B. and Blackfan, K. D.: Clinical and pathological studies in tubular nephritis (nephrosis), Trans. Assoc. Am. Physicians, **44**: 77, 1929.
143. Christian, H. A.: Diseases of the Heart, vol. III, Monographs on Diagnosis and Treatment, Oxford Univ. Press, Am. Branch, New York, 1928.

CHAPTER XIV

ANÆMIA IN BRIGHT'S DISEASE

(Symptoms, Signs, Etiology, Treatment.)

In collaboration with Benjamin I. Ashe

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Introduction

Problem

The recognition that Bright's disease is a systemic or constitutional affection rather than one involving the kidney alone has served to stress the importance of erythrocyte count and hemoglobin determination as an aid in the study of the different forms and stages of this group of maladies. For the description of anæmia as it occurs clinically in nephritic patients we are especially indebted to Dieulafoy[1], Ewing[2], Janeway[3] and Christian and O'Hare[4]. Dieulafoy[1] and other French clinicians spoke of the anæmia accompanying advanced nephritis as "chloro-Brightism". Whether this deserves the distinction of a disease-entity is open to question, but it does serve to indicate that marked anæmia is often found in Bright's disease. In the present volume the anæmia of Bright's disease is considered as a separate clinical problem that demands individual attention apart from the diagnosis and treatment of nephritis, that is, the renal pathology.

Significance

The intensity of anæmia in the various types of Bright's disease is directly proportional to the degree of impairment of

renal function. Brown and Roth[5], in 1922, reporting on 187 cases of chronic glomerular nephritis, demonstrated that a parallel exists between the grade of anæmia and the increasing value of the blood creatinine; they pointed out that the prognostic value of the secondary anæmia was similiar to that of an elevated blood creatinine. In a group of 139 cases those with no anæmia had a mortality in two and a half years of 18 per cent. Those with a hemoglobin of 60 to 85 per cent. showed 46 per cent. mortality, whereas those with less than 60 per cent. had a mortality of 85 per cent. In 1929, Ashe[6] concluded from a study of 300 cases of nephritis and essential hypertension that renal insufficiency, from whatever cause, whether it be secondary to nephritis, polycystic kidney, unilateral nephrectomy or any other reason, is associated with an anæmia that is directly proportional in intensity to the degree of impairment of renal function.

Type of Anæmia

The Blood Count

The blood picture in "nephritic anæmia" varies a great deal. The anæmia may be of the extreme secondary type with a very low color index, or it may be, even at another time in the same patient, of the pernicious type with a positive color index. This anæmia is progressive and often becomes very marked. The following counts are illustrative of the type of blood count met with: in a case of acute diffuse glomerular nephritis, hemoglobin 65 per cent., red cells 3,920,000, color index 0.83; in a case of chronic diffuse glomerular nephritis, hemoglobin 35 per cent., red cells 2,440,000, color index 0.72; in a case of primary contracted kidney, hemoglobin 52 per cent., red cells 3,408,000, color index 0.78 and in another instance, hemoglobin 64 per cent., red cells 3,248,000, color index 1.0.

Blood Morphology

In general, the morphologic study of the red cells reveals microcytes. Macrocytes are found rarely. Berg[7] noted them in but one case with a color index of 0.9 to 1.1, and he reported that Rosenthal had observed them in one instance. In the series studied by Ashe only one patient showed macrocytes; in this case the hemoglobin was 52 per cent., red cells 3,190,000 and color index 0.84; clinically there was a marked hypertension (240 systolic, 150 diastolic), a distinct impairment of renal function and a striking lemon-yellow pallor.

Etiology

Renal Insufficiency

The most frequent and important cause of anæmia in Bright's disease is renal insufficiency. The severity of the anæmia is directly proportional to the degree of impairment of renal function. The data presented in table 55 indicate that no essential difference is encountered in the anæmias of the various forms of Bright's disease provided that renal insufficiency is present. Grouping these cases according to hematuria, edema, albuminuria or hypertension demonstrated that there was no constant relationship of the anæmia to these conditions, but solely to impairment of kidney function. Confirmation of the conclusion that the fundamental factor underlying the anæmia of these victims of Bright's disease is renal insufficiency is afforded by a study of impairment of function associated with polycystic kidney or following unilateral nephrectomy where it is noted that, as in the "medical nephritides", anæmia will occur in those cases that develop renal insufficiency, while it is not found in the patients who, despite the handicap of these

diseases, still maintain good kidney function. For example, one patient with maximal renal insufficiency due to congenital polycystic kidneys had a hemoglobin of 44 per cent. and a red count of 2,728,000 cells and a patient with marked renal insufficiency following unilateral nephrectomy showed a hemoglobin of 45 per cent., with an erythrocyte count of 2,500,000.

Degree of Renal Insufficiency	Type of Disease	Average Hgb. %	Average Red Cell Count
slight or none	acute nephritis	90	4,887,000
moderate		77	4,606,000
marked and maximal		69	3,869,000
slight or none	chronic diffuse nephritis	87	4,759,000
moderate		69	4,083,000
marked and maximal		54	2,944,000
slight or none	hypertension	88	4,848,000
moderate		81	4,763,000
marked and maximal		65	3,775,000
slight or none	myocardial insufficiency with diffuse nephritis	75	4,863,000
moderate		84	4,735,000
marked and maximal		72	4,393,000
slight or none	myocardial insufficiency with hypertension	77	4,881,000
moderate		80	5,044,000
marked and maximal		72	4,250,000
slight or none	hypertension with cerebral pathology	91	5,179,000
moderate and marked		96	5,392,000

TABLE 55. — Blood counts in 300 cases grouped according to the degree of renal insufficiency. The anæmia parallels the extent of impairment of kidney function in all types of uncomplicated renal disease. The "anæmia of hemoglobin only" is apparent in the cases of congestive myocardial failure. The high normal or polycythemic tendency of the "cerebral" cases is also demonstrated.

How Renal Insufficiency Acts to Produce Anæmia

While it has been clearly demonstrated that anæmia is the constant accompaniment of renal insufficiency in Bright's

disease, there is no satisfactory explanation for the concurrence of these two conditions. Considerable suggestive information has been accumulated as to the cause of the anæmia, but the immediate factor responsible for the lowered hemoglobin and diminished red cell count has not been determined. The following have been regarded as possible causes for the anæmia: (1) the effect of albuminuria and edema, (2) the inhibition of the hemopoietic function of the bone marrow through some toxic influence, (3) parenchymatous degeneration of the viscera, particularly the stomach and the liver, resulting in an increased destruction of red blood cells on the one hand and a diminished formation on the other, (4) inanition incident to the low protein diets so often prescribed in the treatment of Bright's disease.

Effect of Albuminuria and Edema. — Writing in the days before tests for renal function were available, Ewing[2] ascribed considerable importance to albuminuria and edema as phenomena "associated with well marked anæmia which, however, is subject to great variation on account of the intermittent course of the disease and of the frequent disturbing effect of treatment. — After the exudative period the blood is partially restored but a certain grade of chlorotic anæmia is apt to persist." While albuminuria may, over a long period of time, be a factor in the production of anæmia in some cases, in others with no albuminuria or edema equally severe anæmia may be encountered. Two cases of moderate albuminuria, followed by Mosenthal for four and six years respectively, showed no anæmia despite the long existence of this abnormal urinary finding. Further discussion of this phase of the etiology will be found under the heading of edematous tubular nephritis.

Toxic Effect on Bone Marrow. — Brown and Roth[5] advanced the theory that defective blood formation due to decreased

function of the bone marrow was responsible for the anæmia in chronic diffuse glomerular nephritis. They did not find the fragility of the red cells increased. The rôle of hemolysis was studied carefully by these workers, who concluded that it was not a factor in accounting for the anæmia. They also decided that the evidence is not yet conclusive that either excessive loss of albumin through the urine, or hydremia can cause anæmia. Christian and O'Hare[4] ascribe the anæmia to a toxic condition rather than to any loss of blood from hematuria, though they mention the effect of this latter factor in some cases of acute diffuse glomerular nephritis.

Parenchymatous Changes. — The effect of parenchymatous changes in many viscera is worth considering as a cause for anæmia in Bright's disease. This perhaps, for reasons to be discussed, deserves special emphasis in the cases with a high color index. Ewing[2], in 1903, attributed the "relatively high hemoglobin index" occurring in chronic exudative (parenchymatous) nephritis to the "loss of albumin which affects principally the serum". He said, "Grave or pernicious anæmia develops in a small proportion of cases of chronic parenchymatous nephritis and appears at times to result directly from the nephritis. It must be referred to the repeated losses of albumin from the blood and to the general disturbance of nutrition, but it is probable that the very severe grades of anæmia result from the combined effects of lesions in several viscera, including gastritis, cirrhosis of the liver, arteriosclerosis, etc." Ewing emphasized the frequency of changes in the liver in cases of Bright's disease, citing capillary distention and congestion and areas of edema as occurring in that organ. Andrews[8] has reported the finding of degeneration of the cytoplasm of the liver cells in dogs with experimental uremia. The first blood-free proteins obtained in

the urine of dogs with "ether nephritides" were found by Andrews and Thomas[9] to be derived from the liver. The fact that the kidney and liver of cattle have been employed so successfully in the recent revolutionary therapy of pernicious anæmia has suggested further the liver as one of the organs that may be involved in the cases of renal insufficiency which exhibit anæmia. Another important parenchymatous change in an organ other than the liver was reported by Janeway[3], who noted the absence of hydrochloric acid in the gastric contents of patients with contracted kidney and anæmia. An absence of free hydrochloric acid was noted in one of the patients described by Berg[7].

Effect of Low-Protein Diet. — This factor will be discussed fully in connection with the treatment of anæmia. A diet of deficient protein content may be necessary because of the demands imposed by a marked renal insufficiency; on the other hand, it frequently is a harmful and useless routine dietary prescription for albuminuria, hypertension or edema.

Anæmia Accompanying the Various Forms of Nephritis

Acute Diffuse Glomerular Nephritis

The causes for a lowering of the percentage of hemoglobin and the number of red blood cells in this condition are hematuria, albuminuria, edema, the toxic effect of the infection responsible for the renal lesion and its complications (e.g., streptococcus sore throat, scarlet fever, influenza, otitis media, etc.), a prolonged period of low protein feeding and renal insufficiency. It is obvious that if the acute nephritis clears up promptly, there will be only a slight degree of anæmia; on the other hand, if the disease is prolonged or becomes chronic, the

lowered quality of the blood may become marked. Van Slyke[4] finds in acute nephritis that the anæmia is directly proportional to the degree and duration of the impairment of renal function.

Subacute Diffuse Glomerular Nephritis

This form of nephritis has a fatal termination within a few weeks to several months after the onset of the disease. The causes for the anæmia are the same as those enumerated for acute diffuse glomerular nephritis. The diminution of hemoglobin and red blood cells, however, becomes much more evident since the condition lasts longer, and renal insufficiency advances rapidly and to such a degree as to be the cause of the patient's death.

Chronic Diffuse Glomerular Nephritis (Compensated, No Impairment of Renal Function)

At this stage, that is, without renal insufficiency, anæmia, when present, may result from the continued use of a diet insufficient in proteins (the restriction having been needlessly imposed) and occasionally from the toxic effect of persistent infectious foci.

Chronic Diffuse Glomerular Nephritis (Decompensated, Secondary Contracted Kidney)

It was in this condition that Brown and Roth[5] demonstrated the parallel between the degree of anæmia and the rising blood creatinine. Increasingly severe grades of diminution in kidney function are matched by increasing anæmia as is shown in the following average figures based on 111 cases of diffuse nephritis reported by Ashe[6]: cases manifesting little or no impairment of renal function (average) hemoglobin per cent. 87, and erythrocyte count 4,759,000; with moderately impaired renal

function, 69 per cent. hemoglobin and 4,083,000 red cells; with marked and maximal renal insufficiency, 54 per cent. hemoglobin and an average red count of 2,944,000. The obligatory limitation of the proteins in the 'diet', as the non-protein nitrogenous materials accumulate in the blood, necessarily aggravate the severity of the anæmia.

Focal Infectious Glomerular Nephritis

Two very prominent factors, both typical of this condition, which operate to induce anæmia are the focus of infection responsible for the nephritis (as sinusitis, etc.) and the characteristic hematuria.

Focal Embolic Glomerular Nephritis

The disease with which this type of kidney lesion is associated, (malignant) infectious endocarditis, will itself produce a progressive and marked anæmia regardless of the severity of the renal lesion. In the vast majority death ensues through septicemia and cardiac failure. Hematuria usually is not sufficiently marked in these cases to affect the blood count, but it may be of considerable importance in a few instances. A small proportion of these patients develop subacute diffuse glomerular nephritis with renal insufficiency. We have already seen how this acts to bring about anæmia.

Albuminous, Anuric and Hypertensive Tubular Nephritis

The presence of anæmia in these conditions depends almost entirely upon the disease which is responsible for the nephritis. Pneumonia, typhoid fever, tuberculosis, carcinoma, bichlorid of mercury poisoning, or toxemia of pregnancy obviously will produce different effects.

Edematous Tubular Nephritis (Genuine Nephrosis)

The diseases with which edematous tubular nephritis is associated often will cause anæmia. Among these are lues, diphtheria, tuberculosis, chronic suppuration and malignant processes. The albuminuria, entailing a diminution of serum-proteins, should depress the red cell count. We have quoted Ewing already as saying that the anæmia of chronic parenchymatous nephritis might be referred "to loss of albumin which affects principally the serum". Barker and Kirk[11], who kept the blood proteins of dogs low for a long time by frequent bleeding, noted a drop in the erythrocyte count despite their returning the washed red blood cells to the dogs they had bled.

It becomes difficult to separate cause and effect in connection with the anæmia of nephrosis, since anæmia itself can cause albuminuria, and since, in long continued anæmia, a lowered total serum-protein is effected. Experimental anæmia by bloodletting also produces lipemia according to Boggs and Morris[12]; the blood fat may rise from 0.3 to 4.53 per cent. of the plasma. Bloor[13] suggests that the cause of this may be due to forcing fat out of the marrow from the stimulation of the function of the blood-forming red marrow of the bones. Mention already has been made of the opinion of Brown and Roth[5] that the evidence is not conclusive that excessive loss of albumin through the urine is capable of inducing anæmia. It is true that Epstein[14] has advocated transfusion as a form of therapy in nephrosis, but this was with the object of restoring the serum-proteins as a step in the treatment of albuminuria and edema rather than with any especial emphasis upon the occurrence of anæmia or the necessity for its treatment. The actual loss of blood protein alone may not be of as great effect

in relation to anæmia, as has been supposed. Recent researches support the view that anæmia does not occur in uncomplicated nephrosis but follows upon the development of renal insufficiency (secondary contracted kidney) in that entity. Wilbur and Brown[15] concluded that anæmia is not observed in nephrosis unless the renal lesion changes to that of secondary contracted kidney with extensive impairment of kidney function; 24 of their 25 cases of "pure" nephrosis (with no renal insufficiency) had no anæmia. In 26 mixed cases (chronic parenchymatous nephritis, contracted kidney), 19 showed anæmia. Mackay and Johnston[16] recently have reported a case of nephrosis of 17 years' duration in which a secondary anæmia was manifested, though there was no clinical evidence of contracted kidney and no nitrogen retention. However, one figure for urea nitrogen of 25 mg. per 100 c.c. is given in the tables published by these workers. Also, as stated by the authors, for almost 15 years this patient's diet must have been greatly deficient in protein. As one reviews the literature relative to the presence or absence of anæmia in nephrosis, it becomes apparent that conflicting reports are probably due to whether or not "pure" or "mixed" cases (with contraction of kidney) are being observed.

A low protein intake may be productive of anæmia in the patient with nephrosis, a condition in which high protein feeding is excellent therapy. This statement does not contradict the previous discussion concerning albuminuria, since the latter factor would be in the nature of possible blood destruction as a cause of anæmia, while the problem of protein in the diet concerns blood formation. Myxedema, with its characteristic edema and cardiac hypertrophy, may be accompanied by anæmia, and this condition may be mistaken for nephrosis with anæmia.

Vascular Nephritis (Compensated, No Impairment of Renal Function)

Here no anæmia occurs unless it is due to unwarranted restriction of protein in the dietary, or to hemorrhages as, for example, epistaxis. When congestive myocardial insufficiency occurs, there may be an anæmia with respect to hemoglobin only, while the red cells are normal or even increased in number due to peripheral stasis.

Vascular Nephritis (Decompensated, Primary Contracted Kidney)

The patients with this type of kidney inevitably will show renal insufficiency and, paralleling that manifestation, an increasing and progressive anæmia. The anæmia associated with pri ary contracted kidney (though this latter condition is not associated with edema, hematuria, infection or appreciable albuminuria) differs in no wise from the blood count in secondary contracted kidney.

Lead and some other metals, which often cause vascular nephritis, are prone to induce anæmia through their action on the bone marrow. Nye[17], of Queensland, Australia, reports anæmia as an early symptom in the chronic nephritis of young people resulting from lead poisoning. Here the disproportion between the degree of anæmia and the extent of impairment of kidney function is due to the fact that the lead induces anæmia before, or apart from, its effect in causing renal insufficiency.

Diagnosis (Interpretation of Blood Count)

It is not intended to convey the impression that all cases of Bright's disease show a well-defined anæmia. In the vast

majority of cases, and certainly throughout most of the course of these diseases, the blood count may be normal. However, with the onset and gradual progress of renal insufficiency, anæmia is inevitable and parallels the extent of impairment of kidney function.

Although renal insufficiency is the most significant factor in the production of anæmia in Bright's disease, certain other possible causes, which have been mentioned for each type of nephritis, must be considered. The more important of these are the infection causing the renal lesion (e.g., scarlet fever or malignant endocarditis), the presence of infectious foci, albuminuria, edema, hematuria and a low protein intake. The blood count may be higher than the corresponding degree of impairment of renal function would lead one to suspect. When this occurs, it may be that the renal insufficiency has not persisted long enough to bring about the anæmia which will follow inevitably. Other exceptions to the rule that the intensity of the anæmia is directly proportional to the degree of renal insufficiency are the "anæmia of hemoglobin only", when there is myocardial insufficiency, and the polycythemic tendency of hypertensive cases with cerebral pathology (see table 55).

Symptomatology

In scarcely any patients with Bright's disease are the symptoms and signs of the anæmia clear cut because the accompanying states, such as cardiac failure, acidosis and uremia, are productive of changes which simulate those engendered by the anæmia. It becomes important to realize that the anæmia, independent of co-existing factors, may be responsible, at least in part, for many symptoms including albuminuria, slight edema, dyspnea, palpitation and a low, fixed, specific gravity

of the urine, simulating the condition as found in instances of marked impairment of renal function. Thus the basis for the hope is furnished that, if the anæmia can be improved, the patient will be relieved of many discomforts, signs and symptoms which impair his efficiency.

The symptoms and signs of the anæmia are similar to those encountered with secondary anæmia under any circumstances and need not be discussed in detail here. A few of them deserve special mention.

The *pallor* of the patient with Bright's disease is well known. The light, lemon yellow color, often combined with a little puffiness of the face, usually suggests the presence of a marked renal insufficiency. Christian and O'Hare[4] refer to the yellowish pallor of the chronic nephritic patient with severe anæmia, the color suggesting that of the victim of pernicious anæmia and standing out in striking contrast to the pale, pasty pallor of the edematous cases of Bright's disease. These authors refer also to the fact that many patients with acute nephritis exhibit a pallor which may at times even be lemon-yellow in hue, yet the hemoglobin and red cell count are normal.

Hemorrhages in the retina, the skin and elsewhere, that are often a serious omen in Bright's disease, may in part at least be attributed to anæmia. The mechanical strain imposed on the arteries by hypertension, embolic phenomena in malignant endocarditis and other forms of septicemia and the toxic effect incident to severe infectious processes are the other factors which must be considered.

The *specific gravity* of the urine in the presence of a severe anæmia is fixed at a level of 1.010. These findings have been discussed in chapter XII on renal function.

The *albuminuria*, the *edema* of the dependent parts and the

dyspnea accompanying a diminution of the hemoglobin and red cell count may be confused with the symptoms of cardiac failure. The albuminuria and anæmia characteristic of myxedema are often diagnosed as Bright's disease.

Finally, there is the possibility that a reduction of the blood may be productive of symptoms that lead to confusion with those of uremia. The two conditions, of course, frequently coexist. Headache, dullness, apathy, nausea, vomiting, vertigo, hallucinations may be enumerated as some of the manifestations that could be attributed either to uremia or anæmia.

Illustrative Cases

Two cases may be cited to illustrate the part played by anæmia in producing symptoms in a victim of Bright's disease. Case I demonstrates the temptation to ascribe to uremia and cardiac failure a group of symptoms produced by marked secondary anæmia in a nephritic.

J. R., man aged 34 years, with a history of chronic diffuse nephritis of about ten years' duration, presented headache, dyspnea, palpitation, slight edema, anorexia and nausea when admitted to the New York Post-Graduate Hospital. On the basis of his past history, his symtoms were ascribed at first to nephritic acidosis, myocardial failure and impending uremia. However, a blood CO_2 combining power of 55 per cent. by volume discredited acidosis as a factor, and the finding of a blood urea nitrogen of only 28.5 mg. per 100 c.c. disposed of uremia as a consideration. The blood count, however, was enlightening with respect to accounting for the patient's state; the hemoglobin was 65 per cent. with 3,200,000 erythrocytes and a color index of 1.01. Transfusion of 850 c.c. of blood was followed by a rise of hemoglobin to 78 per cent. and red cells to

4,480,000 with disappearance of the symptoms which had forced the patient to seek admission to the hospital.

Case II emphasizes the fact that the failure to associate a marked anæmia with impaired renal function may cause a mistaken diagnosis, in this case, of malignancy or internal hemorrhage.

S. M., man aged 49 years, was admitted to the New York Post-Graduate Hospital with a tentative diagnosis or "impression" of a "severe type of anæmia probably due to some internal hemorrhage or new growth". He exhibited a "grapefruit pallor" and an anæmia of 40 per cent. hemoglobin, 3,200,000 red cells and a color index of 0.62. The urine was of 1.010 to 1.014 specific gravity and contained neither albumin nor casts; there was no hematuria. The blood urea nitrogen was 58 mg. per 100 c.c., the blood CO_2 48.7 per cent. by volume. One month later, the blood count was 39 per cent. hemoglobin with 2,080,000 red cells, the color index being almost 1.0. The blood urea nitrogen was now 106 mg. per 100 c.c. and the CO_2 combining power 25.8 per cent. Subsequent autopsy revealed markedly contracted kidneys as the only pathology which might account for the anæmia.

Treatment

Diet

Use of Protein from Point of View of Anæmia. — From the point of view of anæmia, it must be emphasized that the protein content be not too low so far as is consistent with the effect of protein on the kidney and on renal function. Study of the amount of urea metabolized, combined with estimation of blood urea nitrogen and hemoglobin and erythrocyte determinations, will provide the information on the basis of which the protein

in the diet may be so adjusted that the limits imposed by the state of the patient's kidney lesion and renal function will not be exceeded, while at the same time there will be no needless protein restriction. In general, the protein may be "pushed" in the presence of anæmia, until the blood urea nitrogen is about 40 mg. per 100 c.c. with good effect upon the anæmia while, at the same time, no aggravation of the renal lesion or reduction of kidney function are to be expected.

Ability of Nephritic to Utilize Ingested Protein. — The high protein diet in the treatment of nephrosis has met with general acceptance, but high or liberal amounts of protein, consistent with the patient's condition, in the chronic stages of "parenchymatous" or diffuse glomerular nephritis are not yet employed as often as they should be. In hypertensive individuals and in patients with renal arteriosclerosis one meets only too frequently with the empirical curtailment of protein to limits entirely unwarranted by the state of renal function. The effects of feeding huge amounts of protein (in proportion to body weight) to animals, who do not habitually eat either that amount or kind of food, have influenced us erroneously to go to the opposite extreme of too rigid interdiction of proteins in patients with Bright's disease. This, in turn, has had the effect of neglecting the factor of anæmia, so that such a restricted dietary has reduced further the hemoglobin and erythrocyte counts and certainly has not aided recovery from an already existing anæmia. It may be objected that, while proteins will furnish the means of correcting an anæmia, the nephritic patient cannot utilize proteins. There is reason to believe that this suspicion is without foundation. Protein destruction continues even in patients with chronic nephritis, and protein restriction is powerless to prevent this minimal destruction;

in fact, it may increase the amount of body protein that must be metabolized thereby failing to relieve the kidney and, at the same time, increasing the anæmia. In 1916, Mosenthal and Richards[18] fed six patients with moderately severe chronic interstitial nephritis a low protein diet (3 or 4 grams of nitrogen) followed by a high protein diet (21 to 31 grams of nitrogen). A negative nitrogen balance on the low protein diet was changed to a markedly positive balance on high protein feeding. As these workers pointed out, a positive nitrogen balance in nephritis is not necessarily an indication of the inability of the kidneys to excrete nitrogen. Du Bois[19], commenting on this work, makes the remark, "I suspect that most of our nephritic patients are in a condition of partial nitrogen starvation, and that their bodies are eager to replenish these depleted stores, just as in the case of starved normal men, or convalescent typhoid patients."

Ability of Protein to Correct Anæmia. — With the presentation of the evidence of the ability of nephritics to "replenish their depleted protein stores", it next becomes necessary to show that protein feeding is capable of correcting anæmia. It may be said that protein feeding will prevent the occurrence of anæmia or its aggravation in many cases and even will overcome an existing anæmia. Observations in numerous cases, where a period of needless protein restriction has been followed by liberal use of protein, have shown a concurrent improvement in the blood count. The most striking evidence is furnished by Mosenthal[20], who demonstrated that with the establishment of a positive nitrogen balance by high protein feeding in cases of pernicious and secondary anæmia there was a rapid increase in the hemoglobin and erythrocyte count of these patients who previously had a negative nitrogen balance and a marked anæmia.

Foods Other Than Protein Needed to Effect Benefits to be Derived from Protein. — In all individuals, certain rules regarding "protein-sparing" obtain. These have especial significance for the victim of Bright's disease in whom it is necessary to strike a balance between the amount of protein necessary to improve the blood count and the limit which may not be exceeded before undue retention of nitrogen in the blood occurs. Protein, ingested alone, is readily oxidized; it is only with the greatest difficulty deposited to form new tissue. Voit[21] demonstrated that, if that amount of meat be fed which is equivalent to what is oxidized in starvation, nitrogen equilibrium will not be established. Instead, some of the body's flesh will be metabolized also, this latter in steadily decreasing amount if the quantity of ingested meat is gradually increased until finally the point of nitrogen equilibrium is arrived at, at which point the amount of meat which is ingested equals that destroyed in the body. Nitrogen equilibrium cannot be accomplished without carbohydrate in the diet. Thus, Thomas[22] has shown that the feeding of protein alone, given in fractional portions every two hours even to the equivalent of twice the amount of protein destroyed in fasting, fails to establish nitrogen equilibrium. Gelatin spares protein metabolism. The ingestion of 7.5 per cent. of the total heat requirement of the body in the form of gelatin spares 23 per cent. of the body's protein loss, while the ingestion of 60 per cent. of the heat requirement in the form of gelatin will decrease the protein waste only 35 per cent. In the absence of the single amino-acid, tryptophan, nitrogen equilibrium cannot be obtained.

The practical application of these facts, with respect to the use of diet in treating the anæmia of Bright's disease, has been discussed in detail (see chapters XI and XII) and may be

summarized here. The minimal protein quota allowed any patient with Bright's disease should be at least 40 grams daily plus the amount of albumin lost in the urine. If the blood urea nitrogen reaches a level of 40 to 50 mg. per 100 c.c., a lower protein, higher carbohydrate diet should be prescribed. Fats and carbohydrates should be added so that the total number of calories per day is about 2000. Such a food intake may be said to be a preventive measure for anæmia; when a diminished number of red cells is already in evidence, and an anæmia must be cured, the food proteins and calories may well be doubled if the state of renal function permits such an increase. The milk, wheat and cereal diets so widely used in the presence of albuminuria do not contain enough protein qualitatively or quantitatively to maintain health and a sense of well-being and to avoid anæmia. There is no reason why meats or any other foods high in protein content should be abstained from in favor of milk and vegetable products provided the total quantity of protein ingested is wisely regulated.

Medication

With respect to the value of iron and liver extract in treating the anæmia of Bright's disease little information is available in the literature. MacKay and Johnston[16], in describing their patient who gave evidence of having had lipoid nephrosis for 17 years, state that his hemoglobin declined steadily despite high protein feeding and the use of liver extract. Over a period of about two months the patient ingested liver extract equivalent to 600 grams of fresh liver daily. The erythrocytes increased while the liver was taken. The hemoglobin rose following the use of ferrous carbonate (U.S.P.) (Blaud's pills) 0.3 grams three times a day. Christian and O'Hare[4], discussing

acute nephritis, say "with anæmia a little iron helps" and under the heading of chronic nephritis cite Blaud's pills and Basham's mixture (liquor ferri et ammoniæ acetatis) as the forms in which iron may be given. Continued observation and further reports with regard to the effect of liver extract or liver extract combined with iron in remedying the anæmia of Bright's disease would be helpful.

Transfusion of Blood

Why Transfusion Becomes Necessary. — A point is reached in the course of Bright's disease with renal insufficiency when transfusions of blood afford the only means of providing relief of the accompanying anæmia. The time arrives when it becomes impossible to remedy the condition by high protein feeding since retention uremia would undoubtedly follow.

Possible Objections to Transfusion. — A few theoretical objections and impressions still combine to deter physicians from a more general recourse to transfusion of blood in Bright's disease. These objections may be presented as follows:

(*a*) Blood transfusions are thought to elevate the blood pressure.

(*b*) Blood transfusions are thought to produce toxic materials in the body (which a damaged kidney is unable to excrete), and to

(*c*) aggravate the pathologic lesions in the kidney.

The observations of Mosenthal and Ashe[23] show that these fears are unfounded. Transfusions of blood, even up to 1000 c.c., do not increase the blood pressure no matter how high the arterial tension may be. This is of considerable importance in Bright's disease as many of the patients, who are particularly in need of transfusion, may be subject to a marked degree of

hypertension. The theoretical effect of increased blood volume in increasing blood pressure is nullified by compensatory factors (the nervous control of the heart muscle and the larger blood vessels as well as the arterioles) which operate to maintain a constant level of blood pressure despite the change in volume and character of the blood within the limits imposed by transfusion of 1000 c.c. of blood. In the case illustrated in table 56, 1000 c.c. of blood was given within seven minutes by Dr. Lester Unger. Though the effect of the nervous strain incident

Time P.M.	Blood Pressure		Pulse	Remarks
	Syst.	Diast.		
2.35	162	118	84	Lying down; preliminary to transfusion
2.42	228	118	84	Preparing for transfusion
2.45	204	108	90	
2.46	202	116	84	Needle inserted into vein
2.48	228	122	84	300 c.c. blood injected
2.50	226	124	72	500 c.c. blood injected
2.51	228	122	72	700 c.c. blood injected
2.52	224	120	84	850 c.c. blood injected
2.53	220	116	78	1000 c.c. blood injected; transfusion terminated
2.57	226	124	84	Talking about transfusion
2.59	220	122	84	
3.01	212	116	84	
3.07	220	116	84	

TABLE 56. — Effect of Transfusion upon Blood Pressure. February 28, 1930. H. C., male, aged 63 years, suffering from secondary contracted kidney complicated by secondary anæmia; renal insufficiency and hypertension; gout, diabetes mellitus and angina pectoris were also present. The nervous strain incident to the anticipation of the transfusion resulted in a distinct rise in blood pressure. The transfusion of 1000 c.c. (of blood) given rapidly by the direct method did not influence the level of the blood pressure or the pulse rate appreciably. When the apprehension concerning the transfusion was allayed, this patient's blood pressure promptly returned to his habitual level of systolic 160, diastolic 120. (Mosenthal and Ashe[23]).

to preparing for transfusion was to cause a very definite rise in the systolic pressure (from 162 to 228), yet the transfusion

itself did not bring about any increase of arterial tension. Numerous other instances may be cited in proof of the failure of increased blood volume to elevate the blood pressure, of which the following is typical. A man aged 29, with a blood urea nitrogen of 50 mg. to the 100 c.c. of blood and an arterial tension of 230 systolic over 160 diastolic, was transfused, being given 500 c.c. of blood by Unger's method. Throughout the transfusion a blood pressure reading was made each time that 40 c.c. of blood had been introduced. A tension of 230/160 at the start remained unchanged until 400 c.c. of blood had entered the patient's circulation. During the injection of the last 100 c.c. of blood, the pressure was 230/156.

Nor is there evidence that transfusion is responsible for renal damage to any appreciable extent, or more so in victims of Bright's disease as compared to patients free of this malady. The rare untoward effects are largely due to incompatibility of the blood, a defect which more exact knowledge and methods of blood grouping will make even less common. Among these effects are anuria, hemoglobinuria, infarcts of the kidney and tubular nephritis, the result of hemolysis or of anaphylactic shock. On the other hand, instances of relief of anuria by transfusion are reported by Bell[24] and by Ramsay[25], and other cases are recorded in the literature demonstrating that transfusions do not damage the kidney even in the presence of Bright's disease. Reports are available supporting the view that diminution of renal activity following transfusion (in *any* individual) occur chiefly as the result of an incompatibility of the blood of the donor with that of the recipient. Macroscopic cross-agglutination, or direct matching of blood and sera of both donor and recipient, even though both be of the same blood group, and the repetition of this procedure before each

transfusion even if the same donor be employed, will render the likelihood of incompatibility negligible.

Indications for, and Effects of Transfusion. — Having discussed the possible ill effects of transfusion in Bright's disease and shown that they are of very infrequent occurrence and are not especially prone to involve the victim of nephritis as contrasted to the "non-nephritic", we turn to a consideration of the indications which might direct our attention to the use of this therapeutic measure; these are, uremia, edema and anæmia.

Effect on Uremia. — The symptoms of uremia are not alleviated by transfusion, nor has success attended the attempts to first bleed and then transfuse the uremic patient. On the other hand, transfusion does no harm to patients whose blood urea nitrogen is already elevated.

Effect on Edema. — Clausen[26], writing on parenchymatous nephritis, and Epstein[14] on nephrosis, have advocated transfusion to relieve anæmia and, by raising the osmotic pressure of the blood through increase of the blood proteins, to remedy the edema of these states. Further clinical observations with respect to this point are necessary before a final opinion may be expressed. Mosenthal and Ashe[23] failed to relieve edema by many and large transfusions of blood in a case of chronic diffuse glomerular nephritis with a "nephrotic component".

Effect on Anæmia. — Anæmia, the invariable accompaniment of severe and even moderately severe renal insufficiency, is a very definite indication for the use of transfusions, since this anæmia in itself may make the patient an invalid. In these cases, too, it is impossible to remedy the blood deficiency by a high protein diet since retention uremia would be the inevitable sequel. Transfusion carried out when the kidneys are but moderately involved will ameliorate the anæmia for a period of

some months. If this procedure is performed at a time when renal insufficiency is far advanced, relief of the anæmia and its symptoms will be less pronounced and the effect of but short duration. Generally it will be found that three or four successive transfusions of 500 c.c. to 1000 c.c. each, at intervals of about a week, will be necessary before the hemoglobin and red blood cells attain a normal level, and that this regime will require repetition as the anæmia recurs. The earlier in the course of the disease that transfusions are resorted to, the more satisfactory will be the results obtained.

Table 57 illustrates the effect of transfusions carried out

Date 1929	Hb. Per Cent.	R. B. C. Millions	Blood Urea N. Mg./100 c.c.	Blood Transfusion c.c.	Remarks
May 17	69	4.232	38		
24	54	3.110			
29			27	1000	
31	60	3.300			
June 3	60	3.488			
5	62	3.768	43	750	Diet throughout contained 40 to 60 gm. protein a day.
10	70	3.750			
13	80	4.360	45	750	
Sept. 11	72	4.840	25		
Oct. 15	86	5.144	23		
Dec. 10	85	4.536	22		
1930					
Jan. 31	85	4.960	18		
Apr. 25	85	5.232	25		

TABLE 57. — Beneficial Effect of Transfusion on Anæmia. F. F., male, aged 43 years, secondary contracted kidney with a moderate impairment of renal function. The progress of the anæmia was checked by several transfusions; subsequently this patient did very well with a protein intake of 40 to 60 gm. a day. This case serves to illustrate that an anæmia occurring in some forms of Bright's disease may be rapidly, safely and more or less permanently relieved by blood transfusions. When the impairment of renal function is marked, the anæmia recurs, whereas if the kidney eliminates the urinary excretory products satisfactorily, the hemoglobin and red blood cells, as in this case, can be maintained at a normal level for an indefinite period. (Mosenthal and Ashe[23].)

early in the course of Bright's disease. The anæmia had been increasing rapidly, the hemoglobin dropping from 69 per cent. to 54 per cent. and the erythrocytes from 4,232,000 to 3,110,000 within a week. Transfusion served not only to bring the blood count to an approximately normal level but also to check the progress of the anæmia. It would appear from cases, of which the patient described in table 57 is an example, that, early in the course of chronic diffuse glomerular nephritis, when the anæmia and the nitrogen accumulation in the blood are just beginning, transfusions of blood may act to prevent progressive blood destruction and serve as a stimulus for the maintenance of a normal level of hemoglobin and erythrocytes. At any rate, this form of therapy has been given extensive trial by Mosenthal and Ashe[23] and never been found productive of harmful results, while its beneficial effects very often are striking. It may be emphasized that transfusion is here advocated not as a "last resort" in a moribund, uremic patient (in whom the procedure will prove of no avail) but as a means of overcoming the secondary anæmia that often manifests itself long before uremic symptoms appear, and incapacitates the patient who, but for the existence of this remediable symptom, might, despite his chronic Bright's disease, still be active and feeling well.

Summary Regarding Transfusion. — We may summarize our knowledge with respect to the use of the infusion of blood in Bright's disease as follows:

(*a*) Anuria and other effects of transfusion upon the kidney are extremely infrequent and are no more common in patients with Bright's disease than in people with normal kidneys; in some cases it has been observed that transfusion actually overcame an already existing anuria.

(*b*) The kidneys are not injured by transfusion.

(*c*) Transfusions of blood even up to 1000 c.c. do not elevate the blood pressure.

(*d*) Uremia is neither alleviated nor aggravated by transfusion.

(*e*) Transfusions apparently do not exert a diuretic effect.

(*f*) Blood transfusions furnish an excellent means of overcoming the anæmia associated with Bright's disease.

Summary of the Treatment of Anæmia in Bright's Disease

In many forms of Bright's disease the causal factor demands attention to the exclusion of very active treatment of the anæmia. In acute diffuse glomerular nephritis, subacute diffuse glomerular nephritis, focal infectious and embolic nephritis, tubular nephritis of the albuminous, anuric or hypertensive variety, the renal condition and anæmia are so dependent upon the etiologic agent and disease, that therapy must be focused on the primary infection or poisoning. The above varieties of Bright's disease are either of the type of affliction that runs a short, self-limited course, and anæmia then becomes a matter for routine treatment during convalescence; or they are the sequelæ of persistent, often incurable, infectious or malignant disease, when the treatment of the anæmia obviously becomes a secondary consideration.

The problem of preventing and relieving a reduction of the hemoglobin and the red blood cells in chronic diffuse glomerular nephritis, edematous tubular nephritis and vascular nephritis is an entirely different one. In these varieties of Bright's disease anæmia may be favored by hematuria or loss of albumin in the urine or edema fluid, but is the inevitable accompaniment of renal insufficiency when this develops. Since it is appreciated

that impairment of renal function is very likely to come on with these kidney lesions, the preventive treatment is of the greatest importance. This, of course, involves the removal of the cause of the Bright's disease and maintenance of the activities of the kidney, subjects which are discussed in other chapters. The prophylactic and actual treatment of the anæmia are very similar; by what name we wish to designate our therapeutic efforts really depends more on the stage of the disease than on the actual means employed. The point, which it is desired to stress, is that in any form of chronic Bright's disease prevention of anæmia is very necessary if the patient's vitality is to be conserved.

The most important feature of the treatment is to furnish sufficient protein material with which the body may replace the loss of red blood cells and hemoglobin. A minimal protein intake of 40 grams plus the amount lost as albumin in the urine has been advocated. The proteins eaten should not be confined to milk and cereals but should include all varieties, including "white" as well as "red" meats. If anæmia exists, the protein intake may be raised to 60, 80 or even 100 grams. When there is impairment of renal function, the diet should be so regulated that the blood urea nitrogen does not exceed 40, at the utmost 50, mg. per 100 c.c.

Iron medication and liver extract may be employed. Their value in the treatment of the anæmia of Bright's disease has not been fully determined. Arsenic should be used cautiously as it may irritate the kidneys and result in a tubular nephritis.

Transfusions of blood serve to remedy the anæmia and in this way promote the well being of the patient, but they do not relieve uremia or edema, have no salutary effect on the underlying kidney pathology and do not improve the excretory power

of the kidney. Transfusions, especially if used before the anæmia has progressed very far, often restore an invalid to normal activity for a long period. It is usually necessary to carry out several transfusions of 500 to 1000 c.c. of blood each, at an interval of a few days, if the hemoglobin and red blood cells are to be brought to a normal level; nothing short of this goal is worth while.

Bibliography

1. Dieulafoy: Sur le Brightisme, Sem. méd. 282, 1893 quoted in Nothnagel's System of Medicine, Vol. on Blood Diseases, article on Chlorosis.
2. Ewing, J.: Clinical Pathology of the Blood, Lea Bros. & Co., Phila. & N. Y., 1903.
3. Janeway, T. C.: A clinical study of hypertensive cardiovascular disease, Arch. Int. Med., **12**: 755, 1913.
4. Christian, H. A. and O'Hare, J. P.: Nephritis, **3**: 583, Oxford Medicine, Oxford Univ. Press, New York; Nephritis, Cecil's Text-Book of Medicine, 2nd Edition, 927, Saunders, Phila. & London. 1930.
5. Brown, G. E. and Roth, G. M.: The anæmia of chronic nephritis, Arch. Int. Med., **30**: 817, 1922;
   The prognostic value of anemia in nephritis, Jour. Am. Med. Assoc., **81**: 1948, 1923.
6. Ashe, B.: The hemoglobin percentage and the red blood cell count in Bright's disease, myocardial insufficiency and hypertension, Arch. Int. Med., **44**: 506, 1929.
7. Berg, N. N.: Observations on the blood in cases of chronic nephritis associated with nitrogen retention, Am. Jour. Med. Sc., **164**: 88, 1922.
8. Andrews, E.: Experimental uremia, Arch. Int. Med., **40**: 548, 1927.
9. Andrews, E. and Thomas, W. A.: The origin of urinary proteins, Jour. Am. Med. Assoc., **90**: 539, 1928.
10. Van Slyke, D. D. et al.: Bright's Disease, Baltimore, Williams & Wilkins Co., 1930.
11. Barker, M. H. and Kirk, E. J.: Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, Arch. Int. Med., **45**: 319, 1930.

12. Boggs, T. R. and Morris, R. S.: Experimental lipemia in rabbits, Jour. Exper. Med., **11**: 553, 1909.
13. Bloor, W. R.: Plasma lipoids in experimental anemia, Jour. Biol. Chem., **1**: 63, 1925.
14. Epstein, A. A.: Concerning the causation of edema in chronic parenchymatous nephritis: method for its alleviation, Am. Jour. Med. Sc., **164**: 638, 1917.
15. Wilbur, D. L. and Brown, G. E.: The blood in lipoid nephrosis with special reference to the absence of anemia, Arch. Int. Med., **45**: 611, 1930.
16. Mackay, E. M. and Johnston, C.: Lipoid nephrosis: report of a case of unusual duration, Arch. Int. Med., **45**: 734, 1930.
17. Nye, L. J. J.: An investigation of the extraordinary incidence of chronic nephritis in young people in Queensland, Med. Jour. Australia, **2**: 145, 1929.
18. Mosenthal, H. O and Richards, A. E.; The interpretation of a positive nitrogen balance in nephritis, Arch. Int. Med., **17**: 329, 1916.
19. DuBois, E. F.: The control of protein in the diet, Jour. Am. Dietetic Assoc., **4**: 53, 1928.
20. Mosenthal, H. O.: The effect of forced feeding on the nitrogen equilibrium and the blood in pernicious anemia, Johns Hopkins Hospital Bull., **29**: 129, 1918.
21. Voit, C.: L. Hermann's "Handbuch der Physiologie," Leipzig, **6**: pt. 1, 106, 1881; quoted by Lusk, G., Science of Nutrition, 4th Ed., 187, Saunders, Phila. and London, 1928.
22. Thomas, K.: Arch. f. Physiol., Suppl. 249, 1910; quoted by Lusk, G., Science of Nutrition, 4th Ed., 188, Saunders, Phila. and London, 1928.
23. Mosenthal, H. O. and Ashe, B.: Transfusion of blood in Bright's disease, Am. Jour. Med. Sc., **180**: 476, 1930.
24. Bell, W. B.: Treatment of eclampsia by transfusions of blood, Brit. Med. Jour., **1**: 625, 1920.
25. Ramsay, J.: Transfusion of blood in nephritis, Brit. Med. Jour., **1**: 766, 1920.
26. Clausen, S. W.: Parenchymatous nephritis. I. As a general systemic disease, Am. Jour. Dis. Child., **29**: 581, 1925.

CHAPTER XV

BLOOD PRESSURE IN BRIGHT'S DISEASE

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RELATION BETWEEN HYPERTENSION AND DISEASES OF THE KIDNEY

The earliest recognition of an increased blood pressure accompanying Bright's disease was not based on the determination of

the arterial tension itself but on the finding of cardiac hypertrophy. Richard Bright[1], in 1836, in his classical paper, "Cases and Observations Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine", wrote: "The deviations from health in the heart are well worthy of observation: they have been so frequent as to show a most important and intimate connection with the disease of which we are treating: while at the same time there have been twenty-seven cases in which no disease could be detected; and six others, which, from not having been noted, lead to the belief that no important deviation from the normal state existed. The obvious structural changes in the heart have consisted chiefly of hypertrophy, with or without valvular disease; and, what is most striking, out of fifty-two cases of hypertrophy, no valvular disease whatsoever could be detected in thirty-four . . . This naturally leads us to look for some less local cause, for the unusual efforts to which the heart has been impelled; and the two most ready solutions appear to be either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately; or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant sub-divisions of the vascular system."

The cardiac hypertrophy, which Bright ascribed either to the irritating effect of the "altered quality of the blood" or to resistance in "the minute and capillary circulation", gradually has come to be attributed entirely to the latter, or, in more recent clinical terms, to an elevated blood pressure. The conclusions drawn from Bright's observations have proved to be perfectly correct. Many nephritic conditions are accompanied by cardiac hypertrophy, which is brought on by hypertension.

Then the idea came into being that this might not be the entire truth, but that there might also be further causes for hypertrophy of an apparently intact heart and that other clinical states, besides nephritis, might exhibit hypertension.

The cause of cardiac hypertrophy in non-valvular heart disease is a subject intimately related to the problem of increased arterial tension in Bright's disease. At one time the question was debated actively whether the increase in blood pressure was the primary factor resulting in enlargement of the myocardium through the excessive demands put upon it, or whether the vicious circle might have been set in motion by an overactive heart resulting in persistent hypertension. Much has been written on this subject, and it is neither feasible nor profitable to take up this question here in minute detail. The whole problem has been satisfactorily answered by certain researches (the last of these is the work of Burwell and Smith[2]) which have shown that the total cardiac output per minute is the same in hypertensive individuals and in persons with a normal blood pressure. These observations prove, according to Burwell and Smith, that the increase in the work of the heart leading to its hypertrophy in patients with actual hypertension is due not to changes in velocity or cardiac output but to increase in resistance. In Bright's disease, therefore, we may consider that an elevation of the blood pressure occurs for reasons other than disturbed heart action and that cardiac hypertrophy is a phenomenon secondary to hypertension. Another point worth considering is that a rise in blood pressure above the normal dependent on an increased cardiac output or pulse volume, such as we would conceive as the result of a primary heart disturbance, produces an elevation of the systolic pressure only and not of the diastolic. Such a high

pulse pressure has been noted as characteristic for hyperthyroidism and for heart block (see chapter VIII). In Bright's disease, on the other hand, the blood pressure when elevated shows a rise in both the systolic and diastolic values. Consequently, it would appear that the type of hypertension accompanying nephritis is not caused by a disturbance of cardiac function.

Cohnheim[3] formulated the axiom that there is no cardiac hypertrophy without increased work for the heart. This is now generally accepted with a possible reservation in regard to the rarely occurring, so-called idiopathic, cardiac hypertrophy. Thus we may say that all cases of cardiac hypertrophy in the absence of valvular disease of the heart are due either to hyperthyroidism or to vascular hypertension. Most pathologists (see Bell and Clawson[4]) are ready to consider the functional diagnosis of hypertension established on the basis of this anatomical finding at autopsy.

Clinicians as well as pathologists have found that a hypertensive period in life leaves an imprint on the heart that may be read at a later date, even after the blood pressure has been normal for a considerable time. Thus O'Hare, Calhoun and Altnow[5] in a most suggestive article on "the etiology of chronic myocarditis" come to the conclusion that most cases of cardiac hypertrophy, in the absence of hyperthyroidism or valvular disease, are the sequel of arterial hypertension; when the blood pressure is normal or low at the time of a physical examination, reliable confirmatory evidence of previously existing high blood pressure may be found in the eyegrounds. Where hypertension has at any time existed for a longer period, a patient will retain permanent evidence of this in a distinct retinal arteriosclerosis. The criteria for a minimal retinal arteriosclerosis were stipu-

lated as definite irregularity of the lumen of the arteries and compression effects at the arteriovenous crossings.

After all these facts have been considered, and valvular disease, hyperthyroidism and an elevation of the blood pressure have been ruled out, there remain a few instances, very rare in adults, rather more frequent in children, when no adequate explanation can be offered for the existence of a cardiac hypertrophy or a so-called myocarditis. The late John Howland[6] reported a number of such cases in children. The size of the heart was enormous on physical and X-ray examination during life, and at autopsy the myocardium showed hypertrophy only, without any degeneration or infiltration; in every instance there was a disastrous break in cardiac compensation that did not yield to treatment. Howland from his own experience and a survey of the literature believed that these cases of "idiopathic cardiac hypertrophy" are much more common than is generally supposed, and that it is possible to make this diagnosis with a fair amount of certainty, if the symptom complex is kept in mind.

Most clinicians, especially the German authorities, do not recognize idiopathic hypertrophy as a disease of the heart. However, I have seen adult patients and have followed them through to autopsy, who have corresponded in all particulars to the cases of children reported by Howland. I believe that there are many instances of this condition, fulminating in their course, which show a moderate hypertrophy and enlargement of the heart coupled with minor signs of cardiac insufficiency. Christian[7] comes to similar conclusions regarding the existence of chronic non-valvular heart disease occurring without apparent cause.

Thus cardiac hypertrophy in hearts without valvular in-

volvement may be considered in the majority of instances as pointing to a past or present existence of hypertension. There are some exceptions to this rule: marked and prolonged hyperthyroidism will result in heart muscle changes of this sort, and in addition, there are occasional instances where the cause cannot be determined, known as idiopathic cardiac hypertrophy. The enlargement of the heart muscle is clinically demonstrable within about two weeks after the onset of an increased blood pressure; the degree of cardiac hypertrophy is directly proportional to the height of the habitual blood pressure as shown by the observations of Lange and Wehner[8] (see table 33, Chapter IX). The value of estimating the degree of cardiac hypertrophy in any patient with non-valvular heart disease, as a guide to the changes that have occurred in the blood pressure, is therefore very great, though it must be interpreted with certain reservations.

The Relation of Increased Blood Pressure accompanying Nephritis to other Forms of Hypertension. — In 1836 Richard Bright initiated the idea that an elevation of blood pressure accompanies nephritis. The hypertrophy of the heart described by him as characteristic of these cases was the first hint to physicians that the blood pressure could rise significantly above the average normal and be a symptom of clinical importance. Because of the simultaneous introduction of both of these conditions to the medical world by one sponsor, nephritis and hypertension were originally, and in many quarters still are, considered to be inevitably related. The renal factor, giving concrete evidence of disease in its morphological lesions naturally was interpreted to be the cause of the functional abnormality, that is, the rise in arterial tension. Such a linking of hypertension with anatomical renal change and, conversely, the idea that all instances

of elevated blood pressure must be attributed to a kidney lesion, are opinions still held by a number of able and well known teachers of internal medicine.

However, clinical observation has shown that all cases of elevated blood pressure by no means can be put into the same category, and that there are various forms differing from one another in their etiology. How far we may subdivide the types of hypertension depends to a great extent on our conception of the pathological physiology of its production. Such classifications, resting on pathological-physiological, symptomatic or anatomical grounds, have been attempted in a previous chapter (see chapter VIII) and need not be repeated here. It is worth while to consider at this point the types of hypertension that are not a sign of nephritis, as well as those whose dependence on kidney disease is affirmed by some and denied by others.

Forms of Hypertension Definitely not Related to Renal Disturbances. — In a few individuals, the blood pressure maintains a level distinctly above the average normal for no apparent reason. An example of this anomaly is given in table 11 in Chapter II. The systolic blood pressure in this man frequently was at a level of 150 and once at 160, and yet no signs whatsoever of kidney involvement have become evident. This patient has been observed for three years since the table was compiled, thus making a record of 19 years during which a moderate hypertension has existed for no evident cause. Such instances of hypertension, peculiar to some individuals, we have designated as "*constitutional hypertension*" in Chapter VIII. From the extensive observations of Stocks and Karn[9] on the blood pressure levels of normal persons at various ages up to 40 years (table 14, Chapter II) it is evident that a systolic pressure of 160 or over, and a diastolic of 100 or more, is frequently present

in young normal persons. In older individuals, as a result of the physiological changes incident to advancing years, hypertension may become very marked in the absence of any demonstrable pathology in the kidneys. Thus Saller[10] (see table 13, Chapter II) records systolic pressures from 86 to 222 as within normal limits for the age group 68 to 89. Thompson and Todd[11] (see table 15, Chapter II) cite somewhat similar figures for men aged 75 to 92; of 102 systolic blood pressure readings, about 49 per cent. were below 150, or strictly within average normal limits, about 23 per cent. between 150 and 169, about 20 per cent. between 170 and 189, and a few others still higher, in some instances well above 200; the diastolic pressure was within normal limits, that is, less than 90 in about 75 per cent. of the persons examined, between 90 and 110 in about 17 per cent., and higher in the few remaining. From these figures, it is apparent that in old people the systolic pressure is much more prone to be elevated above the average normal than is the diastolic. This is probably the effect of arteriosclerosis, resulting in rigidity and loss of elasticity in the arterial wall. This condition, a part of the physiological process of growing old, necessarily manifests itself in varying degrees. The significance of a high systolic with a low diastolic pressure is a subject of considerable importance in the diagnosis and evaluation of blood pressure and will be taken up in greater detail below.

Constitutional hypertension is found occasionally in young or middle-aged individuals and is common in older persons as a result of changes that may be regarded as physiological variations from the average normal. The possibility of such instances of elevated blood pressure being due to extra-renal factors must be borne in mind when the level of arterial tension is considered in making a diagnosis of nephritis. A hypertension

of this type may be present when there is no nephritis; on the other hand, it may coexist with a nephritis and make the differentiation from a secondary hypertension, that is, one which is the accompaniment of Bright's disease, an exceedingly difficult problem.

A hypertension may be characterized by a rise in either the systolic pressure or the diastolic pressure or both. It is very important to value these figures separately in order to derive the fullest guidance from them. This subject has been discussed in chapter VIII but is reviewed here from another angle, namely, the relation of these various forms of hypertension to Bright's disease.

The least frequent type of elevated blood pressure is that in which the *diastolic element is relatively high, the systolic comparatively low*, and the *pulse pressure consequently diminished*. In Frost's[12] series of observations, only 3.9 per cent. of the cases were in this group. It is commonly acknowledged that this condition is brought on because of *weakening of cardiac power*. Such a change in blood pressure does not occur in every instance of heart failure. The exact determination of the possible effects of myocardial insufficiency on the systolic and diastolic pressures has not been thoroughly worked out. It is a clinical subject worth further elucidation.

When the pulse pressure becomes lowered and when the systolic pressure drops in Bright's disease (provided intercurrent influences such as rest, drugs, hæmorrhage, etc., can be excluded), a serious impairment of circulatory efficiency should be diagnosed. It often foretells death in a few weeks or a few months, although patients with this sign sometimes carry on for a longer period. It is a curious fact that with this bad prognostic sign there is usually little or no immediate parallel

change either subjectively or objectively in such individuals. This shift in blood pressure occurs just as frequently in the patients afflicted with Bright's disease as in those that are free from any nephritic involvement.

There is a group of conditions characterized by a *high pulse or stroke volume*, manifesting itself by an elevation of the systolic pressure, a normal or lowered diastolic and consequently an increased pulse pressure. These conditions invariably should be searched for in any patient whose pulse pressure is in the neighborhood of 60 or higher. They are a very slow pulse rate, usually indicative of heartblock, aortic insufficiency and hyperthyroidism. Very frequently Bright's disease or essential hypertension is diagnosed on the basis of the blood pressure findings. A closer examination often reveals aortic insufficiency and at times excessive thyroid activity as the underlying cause for the elevated blood pressure. The report of Hurxthal[13] shows that in hyperthyroidism the hypertension is temporary, persisting only as long as the increased activity of the thyroid gland, and that it does not lead to "permanent cardiovascular hypertensive disease". In other words, the elevated blood pressure of hyperthyroidism is, in no way, related to that of any of the forms of Bright's disease. It is obvious that the same may be said of the hypertension accompanying aortic insufficiency and heartblock.

Forms of Hypertension that may be Regarded as Secondary to Renal Disturbances. — Under this heading, there are three types to be considered:

1. *A high systolic combined with a high diastolic pressure, both of which are more or less constantly maintained.*

2. *A constantly high systolic and a comparatively low diastolic pressure.*

3. *A high systolic combined with a high diastolic pressure, both of which vary greatly and are associated with definite signs and symptoms of intermittent peripheral vaso-constriction.*

While any of these forms may be found associated with the renal lesions of Bright's disease, there are three widely different opinions on this relationship, namely, that all these types of hypertension depend upon changes in the kidney, that the variations in blood pressure are secondary to nephritis in some instances, while in others they are not, and, finally, that a raised blood pressure is never the sequel of kidney involvement. We believe that nephritis can bring about a rise in blood pressure; the pathological-physiological evidence for this will be reviewed in the next section. From a clinical study of Bright's disease and so-called cardiorenal disease, we believe that hypertension may also exist in the absence of any kidney involvement whatsoever. When an elevated blood pressure is secondary to renal involvement it has definite characteristics conforming to the first type mentioned above, that is, a high systolic combined with a high diastolic pressure, both of which are more or less constantly maintained. The other two types of hypertension mentioned above, namely, the constantly high systolic pressure accompanied by a comparatively low diastolic pressure, and the intermittent instances of elevated blood pressure associated with definite signs of peripheral vaso-constriction, are not, we believe, the result of nephritis, but may be found in combination with the type of hypertension characteristic of nephritis when the causal factors for such variations coexist with Bright's disease. These preliminary statements are made in order to clarify the discussion which follows, regarding these points.

The hypertension characteristic of Bright's disease is distinctly

primarily, and the other one in which the rise in blood pressure is secondary to the kidney pathology. This has led to the designation of two categories of hypertension; (1) primary, (2) secondary.

Recognition of the independence of blood pressure from kidney disease in a certain group of cases dates from a period after the invention of the first clinical instrument for measuring blood pressure, by von Basch in 1876, and was formulated in terms that explain the trend of thought of that time: "latent arteriosclerosis" (von Basch), "presclerosis" (Huchard), "pre-albuminuric stage of Bright's disease" (Mahomed). These names indicate that hypertension may be regarded as a precursor of either arteriosclerosis or Bright's disease. Sir Clifford Allbutt[15] in his work, "Diseases of the Arteries", gives a very graphic account of the considerations for and against these terms and the reasons for his conclusion that there is a disease entity characterized in its early stages by hypertension alone, and which he calls "hyperpiesis". A little later, Theodore Janeway[16] called it "hypertensive cardiovascular disease" because of the serious and frequent occurrence of cardiac failure in this condition. The frequent independence of blood pressure and kidney disease thus has been suspected by a number of clinicians for a considerable time. Such differentiation may be an easy matter today, with adequate tests for renal function at hand, but it was a much more subtle problem when kidney efficiency was necessarily estimated and not determined. Recognition is due the men who were able to put cause and effect into their proper relation, through their sense of clinical values, without the aid of laboratory determinations which now make their theoretical conclusions a certainty. Today the name "essential hypertension", indicating a primary hypertension

of unknown origin, has been generally accepted for this disease.

After this brief and fragmentary review of the types of hypertension and their relation to Bright's disease, it may clarify the subject to add a tabulated summary.

Types of Hypertension and Their Relation to Bright's Disease. — 1. *Constitutional hypertension*, an elevated blood pressure above the average normal, present in some individuals because of their natural physical and physiological characteristics. Such an arterial tension does not increase as time passes and bears no relation to Bright's disease.

2. *An increased systolic accompanied by an increased diastolic pressure.* This form of hypertension is usually the result of an increase in tone of the arteries lying between the heart and the arterioles, associated with a compensatory constriction of the arterioles, regulated so that the blood supply and the blood pressure within the capillaries remain at a normal level in spite of the increase in arterial tension. Such a type of elevated blood pressure may be found in the absence of Bright's disease; it is then known as primary or essential hypertension. It is also the typical form of hypertension accompanying Bright's disease and other kidney affections (see next section for discussion). When it is a usual phase of renal disease, it is spoken of as secondary hypertension. Cases of primary or essential hypertension are far more common than cases of secondary hypertension associated with renal disease. The characteristic levels of a primary, essential or of a secondary hypertension may be modified in various ways by coexisting or complicating affections that result in producing their own peculiar forms of pressure elevation.

These are briefly as follows: an increased systolic accom-

panied by an increased diastolic pressure may at times be the result of an uncontrolled extensive peripheral vaso-constriction. This may be prolonged or intermittent; it may result in symptoms or none, according to the location of the arterioles involved. Convulsions, dyspneic attacks, blanched toes or fingers, etc., are among the frequent symptoms. Such attacks of arteriolar spasm are particularly prone to occur in instances of previously existing hypertension and consequently often modify the blood pressure picture of Bright's disease.

3. *An increased systolic accompanied by a comparatively low diastolic pressure.* This may be due to an increased cardiac output or pulse volume and is often found in aortic insufficiency, hyperthyroidism and accompanying a very slow pulse rate as in heartblock. All these conditions may be present in Bright's disease and consequently may influence the blood pressure.

The usual cause of a relatively low diastolic pressure apparently is the progressive development of arteriosclerosis, involving a loss of elasticity in the arteries with advancing years. This comes about much more rapidly when the blood vessels are under a distinct strain, as they are in hypertensive conditions of any sort. For these reasons, the diastolic blood pressure reading in Bright's disease quite frequently is low.

4. *A low systolic combined with a high diastolic pressure* is characteristic of cardiac failure, which is a common accompaniment of the hypertension of Bright's disease. A marked general weakness serves to lower the blood pressure in Bright's disease. This is commonly noted for several weeks before death occurs in uremic states and is probably the reason for a normal tension or even a hypotension in the insufficient kidney activity accompanying amyloid disease and some of the cases of congenital polycystic kidneys.

The Effect of Involvement of the Urinary Tract (Kidneys, Ureters, Bladder, Urethra) upon Blood Pressure

One of the earliest theories intended to account for the presence of hypertension in Bright's disease, was a purely mechanical one, first advocated by Traube[17] (1856) and later endorsed by Cohnheim[3] (1880); their contention was that a rise in blood pressure was a compensatory phenomenon for the increased resistance opposed to the flow of blood through the diseased renal parenchyma. It is exceedingly difficult, in fact almost impossible, either to confirm or oppose this theory because a great many conditions, both clinical and experimental, have been found in which the circulation of blood through the kidneys may become impeded and with widely different effects upon the level of the arterial pressure. Traube's explanation may prove to be the correct one, though not in the very direct manner in which he thought. The various aspects under which impaired circulation of the kidney may masquerade to affect blood pressure will be taken up briefly in the individual sections which follow.

Retention of Urinary Products in Relation to Blood Pressure

The retention of urinary excretory products and their accumulation within the blood may be regarded as the result of a diminished blood flow through the renal tissues. One of the earliest explanations for the production of hypertension ascribed it to the presence of these substances in the body tissues. Some observers still believe this to be true and consider that the blood pressure fluctuates more or less in direct proportion to the level of blood urea. For instance such an authority as Fahr[18] considers that every instance of renal insufficiency, regardless of its

cause, produces an increase in arterial pressure in direct proportion to the heaping up of non-protein nitrogenous materials in the blood. In acute diffuse glomerular nephritis the hypertension precedes the accumulation of waste products in the blood; in essential hypertension the blood pressure is elevated while the blood chemistry is at a normal level. These facts certainly show that a rise in arterial tension may occur independently of retention of urinary excretory products; however, they do not necessarily prove that there may not be more than one cause for an elevated blood pressure and that one of them may be an increase in the non-protein nitrogenous constituents of the blood. Kylin[19] does not believe this to be true, and neither does the author subscribe to this idea. The reason is that, when the blood urea and the non-protein nitrogen rise or fall markedly in response to dietary regulation, while other conditions are kept constant, the blood pressure in hypertensive patients remains unchanged (Mosenthal[20]). While it must be recognized that renal insufficiency results in both a retention of materials that should be eliminated in the blood and an elevation of blood pressure, yet it is evident that this relation of arterial tension and diminished renal function must be explained on other grounds than the accumulation of non-protein nitrogenous waste products within the body.

Total extirpation of the kidneys in animals usually is reported as having no effect upon blood pressure, (Mosler[21], Backman[22], Hartwich[23]). However, Janeway[24] in analyzing Mosler's results closely finds that of 13 rabbits which survived the removal of both kidneys for 48 hours a rise in carotid blood pressure was observed in all the animals but two, the rise being over 15 mm. mercury in four and 25 mm. in one. It is probable that the depression and shock incidental to the operation of bilateral

nephrectomy would prevent or at least minimize any possible hypertensive reaction in these experiments. Janeway[24] says: "I have seen excision of the only functionating kidney lead to a rise in blood pressure four days after to 180 mm.; it fell again toward death." It is probable, therefore, that complete removal of kidney tissue leads to an increase in arterial tension. The drop of blood pressure as dissolution occurs is noteworthy; such a lowering of pressure nearly always is found with approaching death and is usual in cachectic conditions; this fact is not generally recognized and has led to some erroneous interpretations of the significance of blood pressure. This matter will be discussed in greater detail subsequently.

Partial removal or destruction of the kidneys nearly always results in an elevation of the blood pressure. Pässler and Heinecke[25] found this to be true in animals when, after unilateral nephrectomy, they extirpated a portion of the remaining kidney. Hartwich[23] ligated some renal arteries leaving others intact and noted that a rise of blood pressure ensued. Hartman, Bolliger and Doub[26], by destruction of the kidney tissue in dogs through deep irradiation, induced a marked hypertension. Within a few months the systolic blood pressure rose as high as 220 and the diastolic as high as 150. Janeway[24] some years before had succeeded by reduction of the dog's kidney substance in raising the blood pressure as high as 185 systolic and 150 diastolic 12 weeks after the operative procedure. These two sets of experiments would go very far to show that, when the kidneys are partially destroyed, not only is there a rise in systolic pressure but in diastolic as well. It is this simultaneous rise of both phases of the arterial tension that make it most likely that a hypertension brought about by these means is comparable to that found in Bright's disease.

An impeded urinary flow through obstruction of the ureters or urethra will be followed by a rise in blood pressure. An obstruction that brings this about may be located in the ureters or in the urethra. A partial obstruction of both ureters may bring about an increased blood pressure. Cohnheim[3] in 1880 recorded his observations that cardiac hypertrophy and high arterial pressure followed partial or intermittent obstruction of the ureters. A temporary ligature of the ureters produces a contracted kidney and a hypertension (Rautenberg[27]). I have seen some clinical instances of bilateral stricture of the ureters associated with renal insufficiency and increased blood pressure. Von Monakow[28] reports a case with a calculus in the ureter, whose blood pressure dropped from 170 to 112 after the removal of the stone. Pässler[29] and Brasch[30] report the occurrence of anuria and marked hypertension in women due to bilateral compression of the ureters by pelvic carcinoma. One case of Brasch's showed a rise in blood pressure from 115 systolic to 210 systolic and 160 diastolic after three days of anuria. The arterial tension had a tendency to return to normal when the obstruction was relieved and the flow of urine was reëstablished. Prostatic hypertrophy, by blocking the urethral channel, often results in a rise of blood pressure which frequently subsides as the conditions are restored to normal by retention catheters or operative means (O'Conor[31], Full[32], von Monakow and Mayer[33]). A drop from 180 to a normal level apparently is found frequently under these circumstances; Full records a change of systolic pressure from 230 to 145 in fifteen minutes after evacuation of the urine by catheter. Bell and Pedersen[34] report some interesting experimental results after urethral obstruction: "In one of our experiments a male rabbit developed acute obstruction of the urethra following

repeated catheterization. The blood pressure rose about 40 millimeters of mercury 24 hours later. A similar hypertension was obtained in another rabbit by ligature of the penis." These clinical and experimental observations, as well as those recorded in the section on partial removal or destruction of the renal tissue, furnish indisputable evidence that some disturbances in the kidneys may initiate a process that brings about a hypertension. The patho-physiological course of events is not revealed except for the fact that it is set in motion by a functional or combined functional and anatomical change in the kidney parenchyma.

Diseases of the Kidney in Relation to Blood Pressure

Passive congestion of the kidneys may result in an elevated blood pressure. This is not invariably true but occurs in some instances. Here, as well as in many other conditions to be discussed in the following sections, it may be the lack of power in the cardiac and arterial muscles that make it impossible to respond to the stimulus to augment the arterial tension. Janeway[24] observes that in the later stages of decompensated valvular disease it is the rule to find the blood pressure above the normal, sometimes considerably so. Pedersen (Bell and Pedersen[34]) produced severe chronic passive congestion of one kidney in rabbits by partial constriction of one renal vein. Following this operation, the blood pressure rose slowly and remained well above the normal level for about two months, after which time it returned slowly to normal. The rise recorded in the one experiment charted showed an increase of blood pressure from 130 millimeters of mercury to about 270 in 19 days. It is noteworthy that as the irritation of the kidney disappears and atrophy takes its place, the blood pressure returns to normal. This is paralleled in the case of unilateral nephrectomy in human being, when the blood

pressure does not rise. This would point to some reflex stimulation from the glomeruli, when they are functioning under stress, as one cause for hypertension. When the glomeruli have disappeared, either because of atrophy or through extirpation, the reflex is no longer present, and an elevation of blood pressure is not produced.

Polycystic kidneys furnish an exquisite clinical example of uncomplicated diminution of functioning kidney tissue comparable in many ways to the experimental partial removal or destruction of kidney tissue. If the experimental observations are correct, then there should be a hypertension when the lesion of congenital polycystic kidneys is sufficiently far advanced to eliminate the greater part of the renal tissue from functioning. For a number of years hypertension was regarded as a characteristic sign of this anomaly. In 1917 Means and Rogers[35] published their observations on a case with marked renal insufficiency without hypertension. I followed the blood pressure in one such patient for two years before death and never found it to be above a normal level. Kylin[19] goes so far as to claim that this is the rule and a hypertension the exception. In a recent article on this subject Schacht[36] states: "In a review of 193 cases of polycystic kidney at the Mayo Clinic, one of the most striking abnormalities noted was the number of patients with hyperpiesis." This I believe coincides with the majority of observations made on this disease some years before and not a few months preceding exitus. The renal insufficiency in these cases progresses so slowly compared to that in Bright's disease that they linger for years and tend to develop to a very marked degree the secondary anæmia and cachexia, which Rose Bradford[37] showed was characteristic of an extensive partial nephrectomy. Consequently it is only to be expected that such emaci-

ated persons would not have the cardiac reserve or the muscular tone in the arteries required to produce an elevation of blood pressure. The absence of hypertension, therefore, does not necessarily indicate that the call for such a patho-physiological change is lacking on the part of the kidneys; under these circumstances the significance of low blood pressure in the presence of markedly diminished renal function does not imply that, in a sense at least, hypertension is not produced by such a stimulus.

Amyloid disease of the kidney, at least in the advanced stage of the condition, where many of the glomeruli are destroyed and renal function is very much diminished, according to the experimental results previously mentioned should be accompanied by an elevation of the blood pressure. In this affection the kidneys are the seat of a most extensive vascular lesion and yet, as a rule, the blood pressure has a tendency not only to be at a normal level, but even subnormal. This in all probability is due to debilitated conditions of the cardiac and arterial musculature consequent upon the disease (tuberculosis, chronic suppuration, carcinoma, syphilis are the most frequent) which is the cause of the amyloidosis. Janeway[24] ingeniously suggests the infiltration of the adrenals with amyloid and consequent lack of epinephrin in the body as a possible explanation of the hypotension. This might also be regarded as one of the factors responsible for the debilitated state or cachexia. Hypertension will be found in certain instances of amyloid nephritis, if sufficient power is retained in the heart and arterial muscles to bring this about. Thus Ophüls[38] found that in his series of amyloid nephritis there were three cases of high blood pressure among forty-nine, or 6 per cent.

Tubular nephritis (nephrosis) is, as a rule, not accompanied by an increase in blood pressure. Those who advocate the

dependence of an elevation of arterial tension upon a lesion in the glomeruli believe that the absence of hypertension in *edematous tubular nephritis* (*genuine* or *lipoid nephrosis*) bears out their contention. However, the problem is not as simple as this might seem (if the subject is discussed after considering generalities only and not the exceptions). Wolbach and Blackfan[39] mention systolic pressures as high as 175 in children with this disease, and many authors have recorded such findings in adults. The explanation for a rise in blood pressure may be in the possible involvement of the glomeruli in tubular nephritis. Christian[40] notes that often the glomeruli are obviously involved, while in other cases they probably are not; according to Bell[41] this type of tubular nephritis (lipoid nephrosis) is in reality a form of glomerulonephritis in which the glomeruli are injured; there are many other opinions to the effect that this is a glomerular disease primarily, or coexisting with the tubular affection. It may reasonably be asked why there is only an occasional exhibition of hypertension, and why it is either not constantly present or absent. There are two ways by which these findings may be accounted for, but neither is more than a surmise; either the glomeruli are involved in some instances and not in others, or the strength of the tissues is sapped to such an extent by degenerations throughout the body that the maintenance of an arterial tension at a higher level than normal is not possible. The description of such general tissue changes has recently been given by Alter[42]. Furthermore, there is always the possibility that the rises in blood pressure which do occur may have an extra-renal cause, in spite of the fact that the urine contains albumin and the kidneys show certain pathological lesions.

Bichlorid of mercury poisoning, as is well known, produces a

tubular nephritis, which is complicated by anuria and retention of urinary excretory products frequently with a fatal termination. Theoretically the anuria should be followed by a rise in blood pressure even if the kidney lesion does not bring about such an effect. The hypertension of bichlorid of mercury poisoning usually is absent or slight. Janeway[24] in 1913 made the following statement on this subject: "I have seen the pressure rise from 130 mm. on the first to 168 mm. on the fifth day, remaining about 170 mm. until the ninth day and then fall until death on the thirteenth day. Friedrich Müller reports a similar finding." This notation indicates how, prior to 1913, the blood pressure had been regarded as low in this form of anuria. More recently it has come to pass that most authors claim that hypertension is characteristic of mercury poisoning. It is true that the arterial tension is usually above the normal in this condition, but it does not reach the levels found in essential hypertension or chronic diffuse glomerular nephritis or prostatic obstruction. Here again the depression of vitality incident to the poisoning not only of the kidneys but all the tissues of the body must be a factor in preventing a degree of hypertension which would be assumed, if the cardiac and arterial muscles possessed their full vigor. The drop of blood pressure from the ninth until death on the thirteenth day in Janeway's case is confirmatory evidence on this point.

The *nephritis of pregnancy*, the nephrosis of eclampsia, the nephritic form of the toxemia of pregnancy, has always been a stumbling block to those who wished to account for the occurrence of hypertension on the basis of a glomerular lesion and to consider involvement of the tubules as of no importance in this regard. A marked hypertension is almost universally found in these cases in spite of the fact that glomerular lesions often

are absent (Bell and Pedersen[34]). The blood pressure level in these cases is not slightly elevated, as it is in bichlorid of mercury poisoning or at times in edematous tubular nephritis, but is as high as in any hypertensive condition such as essential hypertension or chronic diffuse glomerular nephritis. Systolic readings in the neighborhood of 200 mm. are the rule rather than the exception. The cause for the increase in arterial tension obviously does not lie in a demonstrable anatomical involvement of the glomeruli. It may be that a functional disturbance of the glomeruli is the spark that initiates the reflex mechanism that results in hypertension. This is equivalent to the theory concerning the elevation of blood pressure that is found clinically or experimentally with oliguria or anuria induced by obstruction of the urinary tract. These are all possibilities, but they have no right to be considered as more than of theoretical importance. Here as well as in other conditions, e.g., essential hypertension, it may be that there is an extra-renal source for the impulse which calls for an increase in arterial tension. This would offer itself as a very plausible explanation.

The level of the blood pressure in *glomerular nephritis* may depend upon the number of glomeruli involved or upon the existence of a diffuse capillary lesion which affects extra-renal tissues as well as the kidneys. Various opinions are held on this matter.

In *focal glomerular nephritis*, the blood pressure usually is at a normal level. In this form of kidney disease only a limited number of glomeruli are affected; furthermore, the lesions are confined to the kidneys, as is shown by the fact that there is no edema. Thus, in focal glomerular nephritis, neither of the causes which theoretically account for an elevation of blood

pressure are present, and no hypertension would be expected.

Acute diffuse glomerular nephritis is accompanied by an increase in blood pressure. Such a hypertension may be very transient, and some authors believe that it may escape notice because of the short period of its existence in some cases. Those who insist that every case of acute diffuse glomerular nephritis is associated with a rise in blood pressure think that it may be found, if the blood pressure readings are made early and at sufficiently frequent intervals in the course of the disease. The hypertension usually is not very marked; the systolic pressure rises to a level of about 150 to 180; the diastolic pressure usually is elevated also. Occasional cases are found where the systolic pressure rises to 200 or higher. Especially in the severe cases the blood pressure may be elevated for a long time and may even persist so as to continue into the chronic stage of the disease. If the acute diffuse glomerular nephritis heals, the blood pressure invariably returns to normal. This usually occurs some time before the albuminuria disappears.

Some authors, as Fahr[18], think that the hypertension here, as in many conditions, is a compensatory phenomenon for the diminished functional activity of the glomeruli. There are some who believe in an entirely extra-renal etiology (Kylin[19], Nonnenbruch[43], Munk[44], Volhard[45], Koch[46], Brasiello[47] and others). They base their contention on the fact that blood pressure readings made in the course of acute tonsillitis and scarlet fever show a rise in arterial tension before the advent of albuminuria. This, however, is not absolute evidence for the time relation between the onset of the inflammation of the kidney and the rise in blood pressure because it is possible, in fact probable, that the earliest renal changes in acute diffuse glomerular

nephritis are not provocative of an albuminuria. The initial lesions in this disease are accompanied by an anæmia of the glomerular capillaries. If there is no circulation in them it is obvious that albuminuria will not be produced. It has been noted in an earlier chapter that the presence or absence of hematuria in nephritis depends upon the maintenance of the blood flow or its cessation; the same reasoning may be applied to the appearance and disappearance of albumin in the urine. A lack of albumin in the urine does not, therefore, necessarily indicate that no nephritis is present, and the finding of hypertension in the absence of albuminuria consequently does not force the conclusion that the rise in blood pressure depends upon extra-renal factors.

Kylin in 1919 demonstrated an increase in capillary pressure, which preceded the rise in arterial tension and the occurrence of albuminuria in cases of nephritis following tonsillitis or scarlet fever. Kylin, largely from this finding, concluded that the condition frequently regarded as "acute nephritis" is in reality a constitutional disease characterized by a body-wide lesion of the capillaries. This work awaits confirmation. In the meantime other investigators (Koch[46], Lange[48], Gobel[49], Boas and Mufson[50]) have failed to obtain a high capillary pressure in acute nephritis. The nature of the extra-renal factors in Bright's disease is still largely a speculative matter. While many of us feel that they are of the greatest importance, yet it must be acknowledged that definite information regarding them is exceedingly scant.

Chronic diffuse glomerular nephritis is characterized by hypertension in most instances. However, it is not always found. It is frequently lacking when renal function is not greatly impaired, and even with marked curtailment of kidney

efficiency it is absent in some cases (Bannick[51], von Monakow[28] and many others). This fact is somewhat disconcerting to those who believe that diminished renal activity is the stimulus that sets up a reflex mechanism, resulting in a rise of blood pressure. There are two points to be taken into consideration in this matter that may account for the lack of a hypertensive response in every case. The first has been mentioned previously to explain the normal or even subnormal arterial tension in amyloid disease and in some cases of polycystic involvement of the kidneys. In these states it is believed that the vitality of the heart and arteries is at such a low ebb that it is not possible to maintain hypertension. In the second place it is only to be expected that the reflex arc resulting in a rise of blood pressure will not function in the same manner in all human beings. This is seen constantly in other reflexes (e.g., in some normal, healthy persons the knee jerks cannot be elicited), and there is no reason why this should not be the case here.

The hypertension accompanying chronic diffuse glomerular nephritis may be accounted for in several ways. There are some authors, represented by Fahr, who believe that there is only one cause for increased blood pressure and that all cases of hypertension in Bright's disease conform to the same type. It seems to us that there are a number of factors incident to nephritis that may be regarded as the provocative agents for an elevated arterial tension. These are all represented in the course of chronic diffuse glomerular nephritis and may well be briefly mentioned here:

1. Chronic diffuse glomerular nephritis undoubtedly begins as the acute form; there may be acute exacerbations at any time during its course, and the chronic stage has many features that are similar to those of the acute form. Consequently the

hypertension of chronic diffuse glomerular nephritis, in part at least, may be ascribed to the same influences, renal and extra-renal, that are active in the acute type. These have been discussed already under acute diffuse glomerular nephritis.

2. In the later stages of chronic nephritis many of the glomeruli become sclerosed and cease to function. Hypertension at this period of the disease is regarded as a compensatory process for diminished renal activity. It is, in many respects, analogous to the increased blood pressure following obstruction of the urinary flow with complete or partial occlusion of the ureters or urethra and has been discussed in that section.

3. A matter which deserves only brief mention is that through the slow breakdown of kidney tissue a toxic material is constantly absorbed in small amounts. This hypothetical substance (renin of Tigerstedt and Bergman) has been credited with being the cause for hypertension. Janeway[24], and all recent authors, discard the idea that "renin" is a factor in elevating blood pressure; he calls attention to the fact that hypertension is most extreme in those exquisitely chronic types of nephritis in which the breaking down of kidney substance must be at a minimum.

4. Finally, the elevated blood pressure may be of the very definite type but of completely unexplained etiology described as essential hypertension in the first half of this book. This form of hypertension, in its initial stages, is not accompanied by nephritis, but later in its course may be complicated by a chronic diffuse glomerular lesion. It is frequently impossible for the clinician or the pathologist to determine whether the hypertension or the nephritis was the primary disease.

An extensive *vascular nephritis* is the sequel of a prolonged elevation of blood pressure, described as essential hypertension

in the first half of the present volume. In only 5 to 10 per cent. of the cases of this prevalent disease does the vascular involvement advance sufficiently to bring about death through renal insufficiency and retention uremia. There is another form of vascular nephritis which develops as a part of a general arteriosclerosis and as a primary condition unaccompanied by hypertension. In its later stages, when kidney function becomes curtailed, the blood pressure may rise, as it does in most cases in which the urinary elimination is diminished.

The Cause of the Hypertension Occurring in Bright's Disease

The cause of the hypertension occurring in Bright's disease can be discussed readily at great length but will be only summarized. From the clinical viewpoint, I believe the most satisfactory diagnoses will be made if we recognize three possible types, each presumably having its own etiology.

1. Essential hypertension, which begins in the absence of any demonstrable kidney involvement and in practically every case brings about varying degrees of renal vascular sclerosis.

2. The blood pressure rise accompanying acute diffuse glomerular nephritis or the kidney of pregnancy. Here, even when renal function is excellent, the blood pressure may be moderately elevated and at times markedly so. This form of hypertension may be due to extra-renal factors, such as a diffuse capillaritis (Kylin[19]), though it must be remembered that this idea is quite hypothetical.

3. Hypertension is secondary to renal insufficiency, whatever its cause. This is true whether diminished urinary elimination is due to obstruction of the urinary tract, polycystic degeneration of the kidneys, or Bright's disease. In certain

conditions in which kidney function is inadequate the blood pressure may not be elevated. This occurs notably in amyloid disease, in some cases of polycystic involvement of the kidneys and in a few instances of Bright's disease. The lack of hypertension in these conditions can be explained by the debilitated condition of the cardiac and arterial muscles that render them powerless to respond to the stimulus calling for an increase in the arterial tension above the normal level.

Loeb[62] in 1905 expressed the idea that the hypertension accompanying renal involvement should be looked upon as a compensatory reflex phenomenon, called into being by the demand for greater activity in the remaining glomeruli. Practically all the theories proposed since that time have restated this same idea in one form or another without advancing it materially. To a certain extent the problem, as to whether or not all hypertension occurring in Bright's disease is secondary to glomerular irritation or destruction, is still an open one. Many observers no longer believe in such a unitarian doctrine but ascribe the production of an elevated pressure to a number of factors as given in the first part of this section.

The Occurrence, Signs, Symptoms and Treatment of Hypertension Accompanying the Various Forms of Nephritis

Glomerular Nephritis

Acute diffuse glomerular nephritis is characterized by a rise in blood pressure. This is usually cited as one of the main differential diagnostic points distinguishing it from the tubular form of kidney involvement. However, too much reliance should not be placed upon this finding as blood pressure may be

normal in the former condition and elevated in the latter. The occurrence of hypertension in acute diffuse glomerular nephritis may be a very transient affair, lasting only for a few days or even only a few hours. Its very short duration in some instances is supposed to account for the fact that it cannot be demonstrated in all cases.

In a girl of 14 the first signs of acute diffuse glomerular nephritis were noted on February 18th; February 19th the blood pressure was 145/65, February 20th it had reached as high as 188/120, while by February 27th it had returned to what may be considered a high normal level of 118/80 for the age of the patient.

On the other hand the hypertension may persist throughout the acute stage and continue into the chronic phase of the disease. A school boy, aged 17, showed signs of acute nephritis on April 1st following an attack of "influenza"; the systolic pressure taken shortly afterwards was 166; 6 weeks later the blood pressure was 148/88, and six months after the onset varied between 142/87 and 176/76; at this time the only other sign of Bright's disease was a faint trace of albumin in the urine; there was no edema, no secondary anæmia, no uremia and renal function was normal.

The level of the arterial tension reached is usually not very high. In a young man aged 22 the blood pressure readings fluctuated between 135/70 and 160/104 during the course of an acute diffuse glomerular nephritis. This is about the degree of hypertension to be expected in this disease. Higher values are found at times; the reading of 188/120 recorded in the case mentioned in the previous paragraph is an example; occasionally a systolic blood pressure of 200 mm. of mercury is found. Whether or not the severity of the Bright's disease is propor-

tional to the height of the blood pressure is an open question. It is certain that the hypertension does not solely parallel the degree of impairment of renal function; it is true that, when there is a retention of urinary excretory products, the blood pressure is high, but the converse, that the arterial tension is normal, when the renal activity is satisfactory, does not hold true. In a previous section it has been mentioned how the rise in blood pressure may precede the albuminuria and the appearance of edema, and that this has given rise to the supposition that the cause for the hypertension may be not only in the kidney but also in the extra-renal factors.

Two sets of symptoms are at times considered to be sequels of the hypertension of acute diffuse glomerular nephritis. These are the so-called uremic manifestation occurring in this disease and cardiac dilatation, which at times is so marked as to entail myocardial insufficiency. Many physicians (for literature consult Oppenheimer and Fishberg[14]) believe that the convulsive seizures, amaurosis and other uremic manifestations of acute nephritis are caused by spasm of the cerebral vessels incident to the hypertension. This may be true, but at best it is only a surmise, and it is worth considering that the toxin derived from the hemolytic streptococcus, which produces the nephritis, may also affect the cerebral tissue and bring about the symptoms in question.

Cardiac decompensation associated with marked dilatation of the heart has been described as the sequel to hypertension in acute diffuse glomerular nephritis. In 1879 Goodhart[53] reported five cases of sudden death from ventricular dilatation in acute nephritis. I. Jesse Levy[54] recently has summarized the fairly extensive literature and case reports on this subject and detailed 10 cases of acute circulatory decompensation compli-

ating acute diffuse glomerular nephritis. He adheres to the explanation that the dilatation of the heart is the result of the sudden development of a hypertension in this form of Bright's disease.

It is difficult to follow his argument that the right chambers of the heart are the first to increase in size and to give way. Clinically, in all cases of high blood pressure in which the heart is affected, the left ventricle is the first to show signs of hypertrophy and, later on, dilatation. There is no reason to suppose that, if the increased arterial tension is the cause for the cardiac dilatation, the right side of the heart should be affected first.

As mentioned previously, it is rare for the blood pressure in acute diffuse glomerular nephritis to assume very high levels. For this reason, as well as for the fact that most of the instances of this type of nephritis occur in young individuals in whom the response of the heart muscle to an increased burden usually is adequate, it seems somewhat improbable that the hypertension should be the cause of the cardiac failure.

Christian and O'Hare[55] believe that the heart is unchanged by acute nephritis except in rare instances when it may be slightly enlarged. They attributed the disturbances in the heart muscle and the consequent phenomena of cardiac decompensation to the same bacterial or toxic agent that caused the nephritis. This would seem the more logical explanation of the occurrence of the occasional cases of dilatation of the heart and cardiac decompensation which accompany acute diffuse glomerular nephritis.

Finally it should be mentioned that it is often a difficult matter to differentiate accurately between acute diffuse glomerular nephritis with secondary cardiac dilatation and decom-

pensation, and primary myocardial degeneration and failure with secondary passive congestion of the kidneys. Some of the cases reported seem to fit in the latter category better than they do in the former. Renal congestion will result in the production of albumin, casts and red blood cells in the urine and often will be the cause of a marked rise in the non-protein nitrogenous constituents in the blood.

The *treatment* of hypertension in acute diffuse glomerular nephritis must confine itself to attention bestowed on the symptoms. The so-called uremic manifestations and the cardiac dilatation may call for energetic symptomatic treatment. Attempts to lower the blood pressure in this condition usually are futile. In most instances the hypertension is not very marked and furthermore it is nearly always transient and, consequently, requires no attention. In the occasional cases, in which the blood pressure is markedly elevated, the indications for control of the arterial tension may be urgent, but symptomatic treatment is the only available recourse at hand.

Sub-acute diffuse glomerular nephritis is accompanied by a slight increase in the blood pressure. The cases reported by Fahr[18] showed systolic values of 155, 100 to 175, 160 and 150 to 172. In one case, a girl of eight years, which we followed for the whole course of the subacute phase of her disease, the highest of 40 readings was 115/80. The arterial tension accompanying this form of nephritis consequently never assumes menacing proportions. Because of the progressively increasing renal insufficiency, a marked hypertension would be expected. However, when the kidney function grows markedly inadequate, the patients are moribund, and their debilitated tissues may not be capable of maintaining a high blood pressure; Hurxthal[13] explained the low arterial tension found in some

with hyperthyroidism on similar grounds. Treatment directed towards control of such mild hypertension is unnecessary.

In *chronic diffuse glomerular nephritis* the blood pressure may be normal or slightly elevated, or there may be a marked hypertension. That the blood pressure may be low, even though there is a distinct renal insufficiency with a high concentration of urinary excretory products in the blood, has been mentioned (Bannick[51] and von Monakow[28]). As a rule, during the early stages of this type of nephritis, the blood pressure is slightly elevated and rises markedly as renal activity becomes curtailed. In other words, the blood pressure may be normal, slightly elevated or markedly raised. These different values may be found irrespective of the presence or absence of edema, secondary anæmia, renal insufficiency or uremia, though, in a general way, the more evident the diminution of renal function becomes, the greater is the hypertension. The following are examples of the various possibilities.

Case 1. Female, age 38. From April 21, 1930 to March 17, 1931, the blood urea nitrogen varied from 31 to 95 mg. per 100 c.c., and 20 blood pressure readings lay between 130/90 and 164/96. *Case 2.* A young man, age 21, was, on complete physical examination including exhaustive tests for renal function, normal in all respects, except for a trace of albumin in the urine and a few hyalin and granular casts; the blood pressure was 120/80; 18 months later, he died of retention uremia; the blood urea N. was at a level of 125 mg. per 100 c.c., and the blood pressure was constantly high, two of the readings being 172/114 and 178/108. *Case 3.* A young woman of 29 was aware that albumin had been present in her urine 12 years ago, and that it had persisted since that time; 6 years ago, kidney function was normal, and the blood pressure was 130/88 to 148/95, that is, it was slightly above the average normal; 2 years ago, there was slight impairment of kidney function (blood urea N. was 20.9 mg. per 100 c.c.), but the blood pressure was enormously increased, being 230/158 and 232/159; subsequently the hypertension persisted at this level more or less until death from retention uremia occurred 2 years later.

The cases of chronic diffuse glomerular nephritis, in which the blood pressure is not elevated, or only moderately so, naturally demand no attention in this regard. Those patients with a marked rise in arterial pressure require treatment for it. This is an intricate problem and since it calls for exactly the same therapeutic measures as essential hypertension, reference is made to that section in the first half of this volume, instead of repeating them at this point.

The late, marked rise of blood pressure in chronic diffuse glomerular nephritis often makes it impossible to conclude whether the case was one in which the hypertension was the primary disease with nephritis as a sequel, or the nephritis was primary with the hypertension as a sequel. In this respect, the pathologist is often as much at a loss as the clinician to determine whether the starting point of the process in the kidneys was in the arteries and arterioles, or in the renal parenchyma. This distinction can be made easily if the physical examinations and tests for renal function are available for a period of years. From another point of view, it may be considered of very little importance which diagnosis is made, because the mode of treatment, the clinical course and the prognosis are identical in the two conditions.

Focal glomerular nephritis is not accompanied by any noteworthy rise of blood pressure.

Tubular Nephritis

In accordance with the classification of this form of renal involvement previously given in chapter XI, the following types may be recognized, albuminuric, edematous, anuric and hypertensive and convulsive tubular nephritis. This subdivision of tubular nephritis was not made on the basis of

particularly characteristic lesions in the kidney, but because the constitutional changes accompanying the renal pathology gave the stamp of individuality to each of these diseases.

Albuminuric tubular nephritis (febrile albuminuria) is not accompanied by a rise in blood pressure. When hypertension is present, there is some other form of kidney involvement or an extra-renal factor to account for it. Thus, blood pressure readings often are a very great help in sensing the presence of acute diffuse glomerular nephritis in infectious diseases, such as pneumonia or typhoid fever, where as a rule only febrile albuminuria is expected.

Edematous tubular nephritis, genuine or lipoid nephrosis, is usually not associated with an elevation of blood pressure. In the few cases I have seen in adults the arterial tension was normal. Fishberg[56] goes so far as to say that a systolic pressure above 130 mm. or a diastolic above 90 mm. should make one suspicious that the case is not one of chronic nephrosis but the nephrotic type of glomerulo-nephritis. Reference has already been made to the observation of Wolbach and Blackfan[39] that systolic pressure as high as 175 may occur in children. While it should be recognized that as a rule there is no hypertension in uncomplicated edematous tubular nephritis, it must be remembered that there are occasional exceptions.

Anuric tubular nephritis for a long time was believed devoid of hypertension. However, during the last fifteen years a study of such cases has shown definitely that as the anuria persists a moderate elevation of the blood pressure to 150 or 180 mm. of mercury is characteristic on the fourth to the sixth day after the poisoning by bichlorid of mercury. Subsequent to this, as the patient either convalesces or succumbs to the anuria, the hypertension subsides and the blood pressure assumes a more

or less normal level. The elevation of the arterial tension is never sufficiently great or prolonged to demand therapeutic attention. It is quite conceivable that the heart muscle, already weakened by the action of the mercury, may not respond as it should to maintain the circulation under the stress of an increased blood pressure, and that recourse to digitalis would be in order.

Hypertensive or convulsive tubular nephritis is a condition that has not been discussed at length in this volume as it is a disease that concerns the obstetrician more than the internist. The blood pressure is prone to be extremely high in spite of the fact that the tubules are the only renal structures which show pathological changes. This is a difficult fact for those to explain who desire to account for all instances of hypertension as a reflex from glomerular irritation. It is possible that this marked increase in blood pressure so often occurring in pregnancy may be the forerunner of a persistent hypertensive state in these patients. This is not always true, but it occurs frequently enough to give rise to speculation regarding the possibility of an acute toxemia as a cause for a permanent functional disturbance resulting in a lasting elevation of the blood pressure. If toxin elaborated during the child-bearing period can bring this about, it is quite conceivable that other poisons or the same poisons at other periods during a life time, may have a similar effect.

Arterial Nephritis

Arterial nephritis or vascular nephritis may come about in two ways; as *the result of degenerative changes* in the kidney, and second as a response to the *strain imposed by arterial hypertension.* Every person is subject to progressive arterio-

sclerosis with advancing years, and the arteries and arterioles of the kidneys are not immune to this process. Consequently, it has become a byword that a normal kidney, on histological examination, does not exist in an adult. These changes in the vessels may progress so that there is a more or less widespread narrowing or obliteration of the arterial lumen and an atrophy of the corresponding portion of the renal parenchyma, resulting in a primary contracted kidney. In such patients, where the disease of the kidney is part of a primary generalized arteriosclerosis (the senile or decrescent arteriosclerosis of Sir Clifford Allbutt), the blood pressure usually is at a normal level. In the early stages of the disease this would be expected; in the later periods, when renal insufficiency supervenes, hypertension may develop, though frequently it is absent. A low or a moderate elevation of the blood pressure under these circumstances may be explained on the basis of a general weakness of the patient afflicted with a diffuse arteriosclerosis.

By far the greater number of instances of arterial nephritis begin as a progressively increasing elevation of the blood pressure without apparent cause, that is, as an essential hypertension. Only after the high blood pressure has, by the strain it imposes on the arteries, affected the arterioles of the kidney does the renal lesion become evident. Vascular nephritis is scarcely ever absent; on the other hand, the changes in the kidney usually are not extensive enough to result in a primary contracted kidney of sufficient severity to produce marked impairment of renal function and uremia. (See discussion in the first half of this volume.) This may be gathered from the fact that less than ten per cent. of all cases of essential hypertension succumb to uremia. The treatment is the same as that accorded essential hypertension, though as renal insufficiency

develops, special allowance must be made for this complication. These two forms of arterial or vascular nephritis fall under the head of benign nephrosclerosis.

Arteriolar necrosis, or *malignant sclerosis of the kidneys* may occur in the course of a marked essential hypertension, especially when the diastolic pressure has been inordinately elevated for a long period. This complication is, as far as we know, invariably fatal, and what therapy should be carried out is an unsolved problem. Thus far symptomatic treatment for the hypertension, the kidney lesions and the progressive renal insufficiency are the only means of combating this disease that have been suggested.

Bibliography

1. Bright, R.: Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine, Guy's Hospital Report, London, **1**: 338, 1836.
2. Burwell, C. S. and Smith, W. C.: The output of the heart in patients with abnormal blood pressures, Jour. Clin. Invest., **7**: 1, 1929.
3. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, 1880.
4. Bell, E. T. and Clawson, B. J.: A study of 420 cases of primary hypertension, Arch. Path., **5**: 939, 1928.
5. O'Hare, J. P., Calhoun, A. W. and Altnow, H. O.: The etiology of chronic myocarditis, Jour. Am. Med. Assoc., **90**: 1436, 1928.
6. Howland, J.: Idiopathic hypertrophy of the heart in young children, Contributions to Medical and Biological Research, dedicated to Sir William Osler, **1**: 582, 1919.
7. Christian, H. A.: Chronic nonvalvular heart disease; its causes, diagnosis and management, Calif. and West. Med., **32**: 320, 1930.
8. Lange, F. and Wehner, E.: Das Herz bei Hypertonie und bei Arteriosklerose, Deutsch. Arch. f. klin. Med., **160**: 45, 1928.
9. Stocks, P. and Karn, M. N.: Blood pressure in early life, a statistical study, Cambridge University Press, London, 1924.
10. Saller, K.: Über die Altersveränderungen des Blutdrucks, Ztschr. f. d. ges. exper. Med., **58**: 683, 1928.

11. Thompson, R. Y. C. and Todd, R. E.: Old age and blood pressure problems, Lancet, **2**: 503, 1922.
12. Frost, H. M.: Hypertension and longevity, Life Insurance Medicine, **1**: 178, 1926. Published by New England Mutual Life Ins. Co., Boston.
13. Hurxthal, L. M.: Blood pressure before and after operation in hyperthyroidism, Arch. Int. Med., **47**: 167, 1931.
14. Oppenheimer, B. S. and Fishberg, A. M.: Hypertensive encephalopathy, Arch. Int. Med., **41**: 264, 1928.
15. Allbutt, Clifford: Diseases of the arteries, London, 1915.
16. Janeway, T. C.: A clinical study of hypertensive cardiovascular disease, Arch. Int. Med., **12**: 755, 1913.
17. Traube, L.: Gesammelte Beiträge, Berlin, 1856.
18. Fahr, T.: Handbuch der speziellen pathologischen Anatomie und Histologie, edited by Henke and Lubarsch, Volume 6, part 1, Berlin, 1925.
19. Kylin, E.: Hypertoniekrankheiten, Second edition, Berlin, 1930.
20. Mosenthal, H. O.: Influence of protein food on increased blood pressure, Am. Jour. Med. Sc., **140**: 808, 1920.
21. Mosler, Ernst: Über Blutdrucksteigerung nach doppelseitiger Nierenextirpation, Ztschr. f. klin. Med., **74**: 297, 1912.
22. Backmann, L.: Einige Versuche über das Verhalten der Blutdruckes nach Nierenentfernung und Nierenverkleinerung, Ztschr. f. d. ges. exper. Med., **4**: 63, 1914.
23. Hartwich, A.: Die Beziehungen zwischen Niere und Blutdruck im Tierexperiment, Verhandl. d. Deutsch. Gesellsch. f. inn. Med., **41**: 187, 1929.
24. Janeway, T. C.: Nephritic hypertension: clinical and experimental studies, Am. Jour. Med. Sc., **145**: 625, 1913.
25. Pässler, H. and Heineke, H.: Versuche zur Pathologie des Morbus Brightei, Verhandl. d. deutsch. Path. Gesellsch., **9**: 99, 1905.
26. Hartman, F. W., Bolliger, A. and Doub, H. P.: The cardiovascular response in experimental nephritis, Jour. Am. Med. Assoc., **89**: 1936, 1927.
27. Rautenberg, E.: Erzeugung chronischer Nierenerkrankungen mit folgender Blutdrucksteigerung und Arteriosklerose, Deutsch. med. Woch., **36**: 551, 1910.
28. von Monakow, P.: Blutdrucksteigerung und Niere, Deutsch. Arch. f. klin. Med., **133**: 129, 1920.
29. Pässler, H.: Beitrag zur Pathologie der Nierenkrankheiten nach

klinischer Beobachtungen bei totales Harnsperre, Deutsch. Arch. f. klin. Med., **187:** 569, 1906.

30. Brasch, W.: Uber die klinischen Erscheinungen bei langendauernder Anurie, Deutsch. Arch. f. klin. Med., **103:** 488, 1911.
31. O'Conor, V. J.: Observations on the blood pressure in cases of prostatic obstruction, Arch. Surg., **1:** 359, 1920.
32. Full, H.: Blutdruck und Harnabflussbehniderung, Berlin klin. Wchnschr., **57:** 1149, 1920.
33. von Monakow, P. and Mayer, F.: Uber den Einfluss der Eschwerung des Harnabflusses auf die Nirenfunktion, Deutsch. Arch. f. klin. Med., **128:** 20, 1918.
34. Bell, E. T. and Pedersen, A. H.: The causes of hypertension, Ann. Int. Med., **4:** 227, 1930.
35. Means, J. H. and Rogers, O. F., Jr.: Observations upon a case of extreme acidosis occurring in a man with bilateral cystic kidneys, Am. Jour. Med. Sc., **153:** 420, 1917.
36. Schacht, F. W.: Hypertension in cases of congenital polycystic kidney, Arch. Int. Med., **47:** 500, 1931.
37. Bradford, R.: The results following partial nephrectomy and the influence of the kidney upon metabolism, Jour. Phys., **23:** 415, 1899.
38. Ophüls, W.: Nephritis and its relation to cardiovascular disease, Jour. Am. Med. Assoc., **96:** 731, 1931.
39. Wolbach, S. B. and Blackfan, K. D.: Clinical and pathological studies on so-called tubular nephritis (nephrosis), Am. Jour. Med. Sc., **180:** 453, 1930.
40. Christian, H. A.: Nephrosis: a critique, Jour. Am. Med. Assoc., **93:** 23, 1929.
41. Bell, E. T.: Lipoid nephrosis, Am. Jour. Path., **5:** 545–684, 1929.
42. Alter, N. M.: The so-called "lipoid nephrosis", Arch. Path., **7:** 1122, 1929.
43. Nonnenbruch, W.: Beobachtungen über die Pathologie und Therapie der Kriegsniere, Ztschr. f. klin. Med., **87:** 397, 1919.
44. Munk, F.: Pathologie und Klinik der Nierenerkrankungen, Berlin, 1925.
45. Volhard, F.: Der arterielle Hochdruck, Verhandl. d. deutsch. Ges. f. inn. Med., **35:** 134, 1923.
46. Koch, F.: Klinische Beobachtungen bei Scharlachnephritis, Ztschr. f. klin. Med., **102:** 182, 1925.
47. Brasiello, E.: Blood pressure elevation preceding scarlatinal ne-

phritis, Policlinico, **36**: 41, 1929, Abstr. Jour. Am. Med. Assoc., **92**: 1640, 1929.

48. Lange, F.: Die Gestalt der Blutkapillaren bei Hypertonien, Deutsch. Arch. f. klin. Med., **152**: 302, 1926.
49. Gobel, I.: Über Schwankungen im Kapillardruck, Klin. Wchnschr., **2**: 2279, 1923.
50. Boas, E. P. and Mufson, I.: The capillary blood pressure in arterial hypertension and in nephritis, Jour. Lab. and Clin. Med., **9**: 152, 1923.
51. Bannick, E. G.: Severe chronic glomerular nephritis without hypertension, cardiac hypertrophy or retinal changes, Arch. Int. Med., **39**: 741, 1927.
52. Loeb, Adam: Über Blutdruck and Herzhypertrophie bei Nephritikern, Deutsch. Arch. f. klin. Med., **85**: 348, 1905.
53. Goodhart, J. F.: Guy's Hospital Reports, **24**: 158, 1879.
54. Levy, I. Jesse: The cardiac response in acute diffuse glomerulonephritis, Am. Heart Jour., **3**: 291, 1930.
55. Christian, H. A. and O'Hare, J. P.: Oxford Medicine, **3**: 674, Oxford Univ. Press, Am. Branch, New York, 1925.
56. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, 1930.

CHAPTER XVI

UREMIA

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DEFINITION, TYPES OF UREMIA

The word uremia was coined, according to various medical historians, to designate either an accumulation of urea or urine in the blood. Which of the two is correct really matters very

little. The name serves to indicate that the original conception of the cause of this disturbance, accompanying Bright's disease, was a retention of urinary excretory products in the blood following deficient renal activity. Since that time, with the development of tests for kidney function, it has been shown that some of the conditions, first described as uremia, are not characterized by an accumulation within the body of urea or other substances ordinarily eliminated through the kidneys.

Cohnheim[1] (1882) thought that all forms of uremia are the sequel of renal insufficiency. This is true in so far that uremia invariably follows a marked curtailment of renal activity, but the converse, that all instances of so-called uremia are secondary to diminished kidney function, is not correct.

Ascoli[2] gave a more ingenious definition of uremia when he described it as "any toxic state or symptom associated with a renal lesion". He strengthened his position a good deal when he said that "it is tempting and justifiable to add, providing no other cause than a disease of the kidney can be found for the toxic state or symptom".

Innumerable definitions of uremia have been formulated and none of them is thoroughly satisfactory. This is especially true because, as we understand this condition at the present time, there is no form of intoxication which is due solely to a retention of urea within the blood. When we consider that there are so-called types of uremia in which there is no renal insufficiency, and furthermore, that, in those instances of uremia in which the renal activity is curtailed, it is not the urea alone that is responsible for the toxic state, it is evident that we have a distressing situation before us as far as nomenclature is concerned. However, through long usage, the term uremia has become so ingrained in medical terminology that it is probably

wise to retain it as a word to describe the nervous symptoms which may develop rapidly or slowly in the course of Bright's disease. Many different forms of uremia, such as visceral uremia, cardiac uremia and asthmatic uremia, have been described. When all of them are considered, it would seem that there are three forms which merit individual consideration. If we accord each the name which describes the condition as it actually exists, these are as follows:

The uremia of

1. *Cerebral arteriosclerosis,*
2. *Acute diffuse glomerular nephritis,*
3. *Renal insufficiency.*

Uremia of Cerebral Arteriosclerosis

Morphological and Functional Pathology

Arteriosclerosis of the brain may be, as in other organs, of two types. The one is incident to advancing years, the other is the result of the strain imposed by hypertension. The former, the *decrescent* or the *degenerative arteriosclerosis* is the cause of the cerebral damage that results in the "chronic uremia" described in the older textbooks of medicine. These patients wander about aimlessly, are unable to concentrate their attention, have a very poor memory, frequently mutter or talk without end and present a rather unchanging picture from day to day. In these cases cerebral hemorrhages and consequent palsies are of rare occurrence. In the uncomplicated cases there is no renal insufficiency and no hypertension, and this condition thus is not the result of Bright's disease and does not belong in the category of uremia as defined here.

The cerebral arteriosclerosis resulting from a persistent and marked elevation of blood pressure presents an entirely different

picture. When arterial tension is elevated over a long period, there usually is a certain amount of cerebral arteriosclerosis. This frequently is silent as far as the production of symptoms go. On the other hand hemorrhages, thromboses, vasospasm, narrowing and obliteration of the blood vessels and small aneurysmal dilatations of the arteries may, one or all, interfere with the functions of the brain, produce irritative symptoms and cause slight or extensive destruction of the brain tissue, that is, *encephalomalacia*. It has been mentioned (Chapter IX) that about 20 per cent. of the deaths in essential hypertension are due to this cause.

Vasospasm of the cerebral vessels as an accompaniment of local arteriosclerosis and a generalized hypertension has been described by Peabody[3], Osler[4], Pal[5], and others. Lately Oppenheimer and Fishberg[6] have called attention to the occurrence of convulsive seizures, transient palsies and other fleeting disturbances, which they ascribe to cerebral angiospasm, and which they believe are prone to occur in hypertensive patients in the absence of any anatomical brain lesions. They have termed this clinical picture hypertensive encephalopathy. From what I have seen in some very careful post-mortem examinations (Mosenthal[7]), I feel that it is often impossible for the physician to know when such symptoms, temporary though they may be, are the result of anatomical damage, which has been compensated for[5], or are caused by a purely functional disturbance, that is an angiospasm of short duration. It is certain that these transient interruptions of the activity of one or the other nerve path are more frequent, when hypertension and cerebral arteriosclerosis coexist, than in the absence of any lesion in the blood vessels of the brain.

The symptoms and signs that occur in some cases of essen-

tial hypertension indicate that there is an increased intracranial pressure at times, especially in the cases of long standing. The terrific headaches, the uncontrollable vomiting and the appearance of choked discs, particularly, point in this direction. The differential diagnosis from brain tumor often is impossible in these cases unless the history of the past few years and the clinical course during that period is given due consideration. It is only to be expected that a wide-spread disease of the blood vessels and the nerve tissue of the brain should result in cerebral swelling and increased intracranial pressure. The wonder of it all is, that it should not occur more frequently.

Signs and Symptoms

Signs and symptoms of the cerebral arteriosclerosis complicating hypertension are extremely varied, as may be gathered from the description of the morphological and functional pathology of this condition. There may be no signs or symptoms whatsoever, and neither the patient's complaints nor a physical examination elicit any indications of the existing disease. When there are evidences of cerebral damage, the signs and symptoms vary a great deal, according to the extent, the location, the persistence and the character of the lesion.

The earlier signs and symptoms have been given in Chapter IX. The condition should not be regarded as the uremia of cerebral arteriosclerosis until it becomes so severe that the patient is confined to bed. These attacks are often fairly prolonged, as may be noted in a patient, 40 years old, a lawyer, who five years before his final attack had a convulsive seizure followed by unconsciousness for half an hour, which was called uremia but was undoubtedly, in large part, of angiospastic origin. The final illness dated from November, 1915, when the

headaches, which had been slight and intermittent, became very much intensified and never left him completely. The systolic blood-pressure varied between 190 and 255. There were several attacks of complete unconsciousness, in each one of which the patient was revived, supposedly by bleeding. On several occasions there was transient motor aphasia with some weakness of the right side of the face. No other palsies were noted. There was a great deal of vomiting, and at intervals there were convulsive seizures. He finally lapsed into a condition of complete unconsciousness; it was impossible to administer nourishment, and he died in October, 1916. At autopsy the cerebral arteriosclerosis was very marked, there were areas of softening and small hemorrhages throughout the brain tissue and small aneurysmal dilatations in some of the vessels.

Patients often have a series of general convulsions, are maniacal and entirely disoriented. When such a condition exists, only a fatal outcome can be expected. It is very remarkable that a temporary, but apparently complete, recovery from these symptoms is possible. There may be a respite for only a day or two at a time, though on several occasions I have seen a return to a normal mental state for a period of about six months, after what had appeared to be a hopeless situation.

Differential Diagnosis

Differential diagnosis from various disorders of the central nervous system may present knotty problems for solution. Brain tumors, purulent, epidemic or tuberculous meningitis, syphilis, acute anterior poliomylitis, encephalitis and many other conditions must be considered. If the antecedent history of hypertension is known, the right diagnosis is often indicated.

Frequently, even with the aid of lumbar puncture, the disease cannot be identified with absolute certainty.

Differentiation from the Uremia of Renal Insufficiency and Acute Nephritis. — If the symptoms and signs of cerebral involvement, such as headache, irritability, palsies, whether transient or permanent, twitchings or convulsions, coexist with a persistently high blood pressure, and there are no signs of markedly impaired renal function, then it is justifiable to assume that a cerebral arteriosclerosis is responsible for these disturbances. Similar clinical pictures may accompany acute diffuse glomerular nephritis; the short duration of the symptoms, the edema and the characteristic urinary findings of acute nephritis make the differential diagnosis from cerebral arteriosclerosis a comparatively simple matter.

Symptoms of Cerebral Arteriosclerosis Formerly Confused with Those due to Renal Insufficiency. — Ascoli's[2] early exposition of uremia describes many instances of transient and permanent palsies. These might involve a single limb, a single group of muscles, or even isolated muscles; there were often hemiplegias or paraplegias. It is now generally agreed that such phenomena are not secondary to renal involvement, that is, nephritis. These occurrences may be due to vasospasm, or they may be the result of small or extensive hemorrhages or thromboses of the cerebral vessels. Both the functional and the anatomical changes are attendant upon hypertension or cerebral arteriosclerosis or both.

Treatment

The treatment of the milder and chronic manifestations has been considered in Chapter IX. The means at our command for the relief of increased intracranial pressure, angiospasm of

the cerebral vessels, anatomical changes of cerebral arteriosclerosis and encephalomalacia are limited and rather ineffectual.

Rest. — The patients should be confined to bed, and absolute rest must be insisted on. This means freedom from visitors, telephone calls, business responsibilities and family worries. Long hours of sleep and control of convulsions, of delirium and of restlessness must be obtained, if possible. There should be a sufficient number of nurses to handle the patient in emergencies; it is common for these patients to get out of bed, shout into the street and carry on in ways that demand forcible restraint, which should be accomplished through human agents rather than irritating mechanical contrivances.

Sedatives often have to be employed. Any sedatives which the physician is accustomed to use are in order. The morphine products will induce constipation and indigestion, and it is best to avoid them if possible. Paraldehyde 15 to 30 c.c. (½ to 1 ounce) by rectum, 4 to 8 c.c. (1 to 2 drachms) by mouth and chloral, up to 4 gm. (60 grains) by rectum and 2 gm. (30 grains) by mouth, may be employed. These two drugs probably are the most serviceable. When hypodermic medications become necessary, hyoscine hydrobromide, 0.6 mgm. (grains 1/100), produces fewer undesirable manifestations than do the morphine derivatives. There need be no hesitation concerning the use of sedatives which achieve the desired end.

Diet. — A moderate caloric intake of simple foods is advisable. Meats and meat products will not raise the blood pressure and are not contraindicated in any way unless the renal function is markedly diminished and in those cases with a polycythemic tendency. An excess of salt should be avoided. When there is vomiting, the feeding must be given in small

amounts at frequent intervals, and at times rectal feeding may become necessary. If the patient is unconscious, excellent results may be obtained by the use of some form of gavage tube through which peptonized milk and eggs, or any liquid product that is required, may be administered. Intravenous use of normal salt solutions or of glucose (10 to 20 per cent.) often is very valuable. The glucose may be given as an accessory food supply. The salt may be used if the sodium chloride of the blood becomes diminished. At least 1½ to 2 liters of fluid should be imbibed during the day. This is necessary for the proper functioning of the skin, the kidneys and the bowels.

Catharsis. — The intestines must be looked after assiduously. Abdominal distention should be prevented. Sufficient cathartic medication should be administered so that the bowel movements are of soft consistency. For the actual cleansing of the lower gut, enemas and irrigations are in order.

Lumbar puncture may be resorted to; symptomatic relief often is obtained by this means. At times, however, it leaves the situation unchanged and occasionally makes it worse. A good effect obtained from one treatment is no guarantee of success if the procedure is repeated.

Vomiting often is difficult to control, as it is of central origin. If it is frequent and persistent enough to prevent the proper intake of food, care must be taken that substitute paths of intake are provided as detailed in the paragraph on diet. The sedatives, the lumbar puncture and other forms of therapy for control of the blood pressure and the circulation within the brain should be effective for relief from the vomiting, if any means will accomplish this.

Venesection should be performed if the hemoglobin and the red blood cells are high. It should not be attempted if the

hemoglobin is less than 80 per cent. and the red blood corpuscles less than 4,500,000 per cu. mm. Bleeding may lower the blood pressure, though usually not to any great extent; it may relieve over-strain on the heart; it often makes the patient feel much less clouded mentally, and may add considerably to his well being.

Cardiac decompensation should be looked for carefully. If it exists at all, there should be no hesitancy in resorting to digitalis despite the hypertension and cerebral symptoms. There is much less strain upon the vessels of the brain, when venous congestion is relieved, and the blood circulates properly. Even during coma these principles should be followed.

Hypertension. — As stated in the section on hypertension (Chapter IX), there is no known method at present for the satisfactory control of hypertension. The formula of administering iodides or vasodilators and resorting to venesection may be tried. Sedatives and rest probably accomplish more than any other means of treatment. Magnesium sulphate has been advocated recently by Blackfan[9] for the control of intracranial pressure and increased arterial tension. The methods of using this drug and other therapeutic procedures will be given in the section on the treatment of the uremia of acute diffuse glomerular nephritis.

Blood Chemistry as a Guide to Treatment. — It is worth while at frequent intervals to determine the chloride and the urea content of the blood and the CO_2 combining power of the plasma. If the sodium chloride rises inordinately or drops, corresponding measures should be taken in the diet to correct such an abnormality. A rise in the blood urea nitrogen to a point above 40 mg. per 100 c.c. indicates that kidney function should be considered, and that possibly the proteins in the diet

should be curtailed. An abnormally high carbon dioxide combining power of the blood, indicative of alkalosis, may occur as the result of vomiting or overdosing with alkalis. Sometimes this may become the cause for renal insufficiency (see table 38 detailing a case with normal renal function in which the urea nitrogen rose to 63, the uric acid to 8 and the creatinine to 4.3 because an alkalosis existed) and may result fatally unless corrected by the use of hydrochloric acid or acid phosphate salts by mouth or rectum, or by other means that suggest themselves to prevent vomiting and to supply acid material. If an acidosis exists, as indicated by a diminished CO_2 combining power of the plasma, bicarbonate of soda or other alkalis are indicated, but care must be taken that the condition is not over-corrected and an alkalosis produced. Eight to twelve grams (2 to 3 drachms) of bicarbonate of soda a day usually are sufficient to bring about the desired effect, and the large amounts of alkali which have been used with severe acidosis in other conditions are out of place.

Uremia of Acute Diffuse Glomerular Nephritis

Definition

When studies in blood chemistry were first extensively carried out, beginning about 1915, it became apparent, much to the surprise of nearly all physicians, that the uremia accompanying acute diffuse glomerular nephritis, or acute exacerbations of chronic nephritis, was not accompanied by a noteworthy increment in the blood urea. In other words, renal insufficiency and the retention of urinary excretory products were, contrary to the prevalent belief, not responsible for this type of intoxication in Bright's disease. In addition, it was soon noted that convulsions and spastic phenomena were much more common

and much more marked than in the uremia associated with failing activity of the kidney. Consequently the uremia of acute nephritis has been variously called the convulsive, the epileptiform, or the sthenic form of uremia to differentiate it from the asthenic or the retention uremia following upon insufficient urinary elimination. Since neither the cause nor the pathology of this symptom complex has been satisfactorily explained, it is preferable to think of it in terms that state the facts as they are known at present and call it the uremia of acute nephritis.

Etiology, Morphological and Functional Pathology

There are three explanations of this form of uremia that merit attention. These are:

1. Edema of the brain,
2. Angiospasm of the cerebral vessels,
3. Damage of the brain by the hemolytic streptococcus toxin, which also is the cause of the nephritis.

Cerebral edema has, for many years, been thought of as a cause of uremia. Traube[8] in 1861, at a time when all the disturbances of the central nervous system manifesting themselves in the course of Bright's disease were believed to be identical, formulated the theory that edema of the brain was the pathological lesion that was responsible for the uremia manifestations. Cohnheim[1] (1882) did not subscribe to this idea because he failed to find cerebral edema in many cases of uremia. He did not realize that, what was at that time described as uremia, was in reality not an entity but a group of conditions, which differed from each other very widely both in regard to etiology and pathology, and that any attempt to unify them in these respects necessarily must prove to be futile. Blackfan[9]

and his associates recently have revived the idea that edema of the brain is responsible for the uremia accompanying acute diffuse glomerular nephritis, but not for the other uremic states.

The brain was markedly edematous, the convolutions flattened, the sulci indistinct and the medulla compressed in the cases of Blackfan[9] that were examined at autopsy. As might be expected, lumbar puncture yields a large amount of cerebrospinal fluid under greatly augmented pressure. Cushing[10] has shown that an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against that of the medulla. This is stressed because Blackfan[9], with good reason, utilizes the blood pressure as an index of the necessity for treatment of the cerebral edema. The other symptoms of the uremia of acute diffuse nephritis such as vomiting, headache, visual disturbances, convulsions are all ascribed to the rise in intracranial pressure accompanying the cerebral edema.

The edematous condition of the brain is, to a certain extent at least, an unsatisfactory explanation for the uremia in acute nephritis because cerebral edema in itself is not a primary affection but must be the sequel of some other injury. A wet brain consequently is a cause within a cause; it is a symptom or sign which carries other symptoms or signs in its train. The original thought of Traube[8] was that the edema depends on two factors, the elevated arterial pressure and the disturbed osmotic relations entailed by the diminished protein content of the blood. Both of these are now known not to hold true. Marked hypertension and advanced degrees of anemia occur without any accompanying cerebral edema. Either the constitutional tendency to edema in acute nephritis, or the effect of the hemolytic streptococus toxin, which is the cause for the

lesions in the kidneys, or both of these may be contributory factors in bringing about an edematous condition of the brain.

A marked fluctuation in the concentration of the substances in the blood that control the interchange of water between the tissues and the blood and lymph might be regarded as causes. However, these changes are hardly ever drastic enough to bring about such an effect and, even with the extreme elevations of the substances as determined by routine blood chemical examinations in the terminal stages of retention uremia, edema of the brain is not found. Andrews[11] succeeded in producing a wet brain and symptoms resembling those of uremia by the injection of hypertonic salt solutions, but it is doubtful whether such sudden and extreme stimuli, which forbid compensatory adjustments, are found as the result of the morbid processes accompanying any form of Bright's disease. While we are not aware of what derangements are the cause of edema of the brain and can thus far only theorize concerning them, it is evident that this cerebral affection has been shown by Blackfan[9] to accompany acute diffuse glomerular nephritis, and that it may be responsible for the uremic manifestations associated with that form of nephritis.

Angiospasm. — The possibility that various symptoms due to dysfunction of the central nervous system may be caused by a temporary contraction of the cerebral arteries has been described already under the heading of uremia of cerebral arteriosclerosis. Oppenheimer and Fishberg[6], in their recent review of vasospastic phenomena accompanying hypertension, have advanced the theory that the convulsions, amaurosis and other transient symptoms of central nervous system involvement, which constitute the syndrome of convulsive, sthenic or epileptiform uremia in acute nephritis, are all brought on by

angiospasm of the cerebral arteries. The brain itself is supposed to be without anatomical change. This condition has been named hypertensive encephalopathy. In the previous section Blackfan[9] has been quoted as demonstrating the presence of cerebral edema as a possible pathological lesion of the brain. The duration of such symptoms as blindness in acute nephritis is frequently as long as 24 or 48 hours. These findings, in the absence of conclusive proof that vasospasm is solely responsible for the nervous disturbances of acute nephritis, point to the possibility of spasm of the cerebral arteries as being an accessory phenomenon in the production of the uremia, but they cast considerable doubt on the likelihood of accounting for the entire symptom complex on this basis.

The toxin derived from the hemolytic streptococcus, i.e., the same toxin that is responsible for the changes in the kidney, has to be considered as a possible cause of the cerebral damage resulting in the production of the uremia accompanying acute diffuse glomerular nephritis. The pathological lesions in the brain might very well be the result of poisoning from this source, especially as Blackfan[9] mentions numerous pinpoint hemorrhages throughout the brain substance as one of the characteristic findings. Angiospasm might be brought about by the same factor. The theory that attributes the inflammatory and irritative lesions in the brain to the same bacterial toxin as the one that produces the changes in the kidneys has much to be said for it. Similar cerebral symptoms follow various bacterial invasions of the central nervous system, such as meningitis, encephalitis, anterior poliomyelitis, and the differential diagnosis between these diseases and acute diffuse glomerular nephritis often is extremely difficult during the first day or two of observation. Furthermore, there is the lure of

simplicity and common sense when the lesions in the kidneys and those in the central nervous system are ascribed to a single etiological factor. For all these reasons it may be considered probable that the toxin derived from the hemolytic streptococcus is the causative agent for the cerebral involvement that results in the uremic syndrome of acute diffuse glomerular nephritis. This does not claim that the edema of the brain (Blackfan[9]) and angiospasm of the cerebral vessels (Oppenheimer and Fishberg[6]) are to be set aside as causative agents, but that the hemolytic streptococcus brings about the changes described by these authors and presumably other disturbances as well. It seems certain that these symptoms are not secondary to the involvement of the kidneys, but occur as an independent condition due to anatomical and functional disturbances of the central nervous system.

Diagnosis, Symptoms and Signs

Diagnosis. — The existence of an acute diffuse glomerular nephritis must be established in the first place. There is the history of an infection, mild or severe, with the hemolytic streptococcus, such as scarlet fever, tonsillitis, pharyngitis, or fever without a demonstrable local invasion that usually is called influenza, etc. In addition hematuria and red blood cell casts, an elevation of the blood pressure, some edema, especially about the face, a urine of small volume and high specific gravity and a moderate or no rise in the blood urea are the diagnostic features. In essence, if we regard the streptococcus toxin as responsible for this form of uremia, there should not be a great clinical difference between the encephalitis here and that in other diseases, with one possible exception, and that is the rapid healing of the brain lesions, when the production of the

toxin subsides, whereas in the actual bacterial invasions there is much more likely to be a residual impairment, the prognosis is not so favorable and recovery, when it does occur, is likely to be much slower. However, these differential diagnostic points are all of late occurrence in the course of these diseases, and the fact remains that the only means of early diagnosis of the uremia of acute diffuse glomerular nephritis, in the presence of undoubted signs of encephalitis, is the demonstration of a coexisting acute diffuse glomerular nephritis.

The *signs* and *symptoms* ascribed to the uremia are exclusively those brought on by cerebral involvement (headache, vomiting, convulsions, coma). The signs of the concomitant acute nephritis are present as well. The occurrence of generalized *convulsions* always has been regarded as the salient feature of the uremia of acute diffuse glomerular nephritis, and consequently it has also been called convulsive, sthenic or epileptiform uremia. The convulsions come on suddenly, are severe, epileptiform in character and last for a few minutes. There may be only isolated convulsions, or they may recur very frequently. The patient may be conscious throughout, though usually *coma* is present during the convulsive period. *Headache* and *vomiting* are among the first symptoms and as a rule occur before coma begins. *Loss of vision* is a very distressing symptom; this is known as nephritic amaurosis. The eye itself, including the retina is negative on examination, thus pointing to a lesion in the brain or the optic nerve. The amaurosis usually disappears completely within about two days.

One of the diagnostic features of the condition is that the *blood chemistry*, the urea, the non-protein nitrogen, the creatinin, etc., are only slightly to moderately elevated, and the CO_2 combining power of the blood is not very much depressed.

This serves to distinguish this form of uremia from that due to renal insufficiency. At times, when an attack of acute diffuse glomerular nephritis occurs as a complication in a patient suffering with an advanced primary or secondary contracted kidney, both types of uremia, that of acute nephritis and that of renal insufficiency, may cœxist, and it may be a difficult matter to separate the signs and symptoms of the two very accurately.

The *blood pressure* usually is elevated. There is a rise in both the systolic and diastolic readings. The systolic pressure may rise to 200 mm. of mercury or higher. It is well known that the hypertension in acute nephritis is very transient. Blackfan[9] stresses the idea, and it is a very suggestive one, that the increase in arterial tension may be directly proportional to the degree of intracranial pressure and consequently that the rise or fall in blood pressure furnishes a good guide as to the success of, and necessity for, therapeutic interference.

Clinical Course and Prognosis

The onset of this condition is sudden and the course a rapid one. The uremic symptoms of acute diffuse glomerular nephritis usually subside within two or three days after their appearance. The prognosis for recovery from acute diffuse glomerular nephritis, as far as the uremia and immediate vitality are concerned, is very good. Death occurs but rarely as the result of the uremic seizures, though Blackfan[9] reports three deaths in a series of 24 cases. It is probable that the fatal termination is due to the persistent multiplication and growth of the hemolytic streptococci at the original site of the infection rather than to any other factor. Thus, it is a mistake to think of the uremia as responsible for a fatal issue, because it is solely a secondary phenomenon brought on by toxic invasion

of the brain by bacterial products which are produced at the primary seat of the disease. The following case (table 58) illustrates many of these facts.

Feb. 19 — 1 day ago swelling of face and eyes; became blind; 6 convulsions; eye grounds normal. B. P. 145/65, edema of face and legs, unconscious.

Feb. 20 — Blood urea N 16.0, creatinine 2.1, phthalein test 42%, B. P. 188/120.

Feb. 23 — Severe convulsion. Urine: large amount albumin, hyaline and granular casts.

Feb. 25 — Urea N 13.5 (spinal fluid); phthalein test 50%.

Feb. 27 — Blood urea N 14.7, creatinine 1.9, B. P. 118/80.

Mar. 3 — Complete recovery except for albuminuria and casts.

TABLE 58. — Uremia of acute diffuse glomerular nephritis in a boy aged 14. Note the short duration of the hypertension, convulsions, blindness and coma and the complete recovery from these affections; the kidneys function at an approximately normal level throughout the uremic seizure.

Treatment

The treatment of the uremia of acute diffuse glomerular nephritis presupposes that everything possible is being done to combat the primary hemolytic streptococcus infection. It must be recognized that the immediate therapy of this condition is purely symptomatic, and that the involvement of the brain will not subside because of local control but only when the activity of the primary focus ceases. It is very necessary at times to limit the exhaustion induced by persistent headache, vomiting and convulsions, but apart from that interference it has seemed to me doubtful whether the uremia of acute diffuse glomerular nephritis can be influenced in its course by therapeutic efforts. Fortunately the condition generally is self-limited; in other words, the distressing symptoms are

prone to disappear spontaneously within three to six days (see table 58). Excellent results have been obtained in the handling of this syndrome by many modes of procedure. In fact the results have been so uniformly satisfactory that the statement just made concerning the tendency to spontaneous recovery seems warranted.

The acute nephritis (lesion in the kidneys) must be treated according to the principles laid down in Chapter XI.

The convulsions and other irritative symptoms of the central nervous system must never be allowed to become so severe as to cause harm. It is better to institute symptomatic treatment for their control too early than too late.

Physical Therapy. — Hot baths often have a remarkably soothing effect. They may be given for 10 to 15 minutes at a time and can be repeated every 4 hours. The eliminative treatment by hot packs and electric light baths of various kinds are of doubtful value. Rectal irrigations, Murphy drips, retention enemata or gavage procedures are indicated, if it becomes necessary to administer food and especially fluids by artificial means. If these fail, infusions or hypodermoclyses may have to be employed. Transfusions or venesection are rarely indicated in the treatment of the uremia of acute diffuse glomerular nephritis.

Sedatives are often necessary to control severe convulsions. Chloroform by inhalation has been used successfully to check each convulsion as it arises. Chloral, 1.3 to 4 gm. (grains 20 to 60) and paraldehyde, 8 to 30 c.c. (drachms 2 to ounces 1) by mouth or rectum are among the preferable drugs. They may be used in large doses without fear of causing any harm. Any sedatives one may choose are acceptable. The morphine products, once excluded because they were thought to inhibit the

activity of the kidney, are coming back into favor since they have been found not to depress the kidney function.

It is a thankless and unnecessary measure to recommend particular sedatives to individual physicians or to drug houses. There is room for personal preferences since all accomplish the desired result. I have hesitatingly expressed my own choice at the beginning of this paragraph.

Blackfan[9] has advocated the use of *magnesium sulphate* by mouth, rectum and intravenously. This has been tried by others (Calvin[12]) and found to be satisfactory. The exact mode of action of magnesium sulphate is not clear; there may be some sedative effect, though the amount administered is not sufficient to suppress the convulsions; there is supposed to be a considerable withdrawal of water from the brain because of the osmotic action of the hypertonic magnesium sulphate solution in the blood. Blackfan[9] considers a rising blood pressure as a danger signal and that the magnesium sulphate must be used with all dispatch to check the rise in intracranial pressure of which the hypertension is a signal. In children 30 to 45 c.c. (1 to 1½ ounces) of a 50 per cent. solution of magnesium sulphate is given by mouth every 4 to 6 hours, and about 90 c.c. (3 ounces) of the same solution by rectum every 6 hours. A 1 per cent. solution of magnesium sulphate is used for infusion. The intravenous injection is made at a rate of 2 c.c. per minute. About 15 c.c. per kg. (2.2 lbs.) is given in children, or the blood pressure may be taken as an indicator of the need for continuing the infusion. It may be stopped when the systolic blood pressure falls to 120. The effect of the infusion lasts 5 to 12 hours, and it may be repeated every 12 to 24 hours for several days if necessary.

For the reduction of increased intracranial pressure the use of hypertonic dextrose, a 50 per cent. solution, has been recommended (Kennedy and Wortis[13]). One hundred c.c. of this solution may be given intravenously two or three times during 24 hours. I have not seen this used in the treatment of the uremia of acute diffuse glomerular nephritis. Theoretically it should be of value.

Uremia of Renal Insufficiency

Definition

The original conception of uremia was that all toxic symtoms accompanying diseases of the kidney and the urinary tract were due to a deficient elimination of urine. The study of renal function during the last 15 years has made it clear that there was more than one type of intoxication included in the original concept of uremia. The uremia of cerebral arteriosclerosis and of acute diffuse glomerular nephritis have been described already; they are very different in their etiology and symptomatology from the uremia of renal insufficiency.

In reality the name uremia should be restricted to the uremia of renal insufficiency, and even here its appropriateness is somewhat doubtful. If it signifies that the retention of urea in the blood and tissues is the cause of the toxic condition, it is a misnomer; if it is regarded as indicating a deficient urinary elimination and consequent poisoning through retention of many, if not all, of the urinary excretory products, the term is more nearly correct. Consequently the uremia of renal insufficiency has also been called retention uremia; it is also known as asthenic uremia, to distinguish it from the sthenic, convulsive or epileptiform uremia of acute diffuse glomerular nephritis.

Morphological Pathology

General Condition. — There is a marked pallor due to the anemia which usually accompanies an advanced degree of renal insufficiency (Ashe[14]). A lemon yellow tint is frequently present in the skin and scleræ. This is probably the result of hemolysis. A slight puffiness about the face and some edema of the other parts of the body, such as frequently accompany severe anemia, is often in evidence, though the marked and generalized edema, the anasarca, characteristic of the earlier stages of chronic diffuse glomerular nephritis and edematous tubular nephritis, is rarely found.

The body is poorly nourished and, in many instances, of cachectic appearance. This is in part due to the malnutrition following on loss of appetite and vomiting, though the prevalent use of very low protein diets in the treatment of Bright's disease is undoubtedly responsible to a certain extent; in part, it is caused by the rapidly developing cachexia attendant upon the cessation of function and the destruction of large amounts of kidney tissue, as demonstrated by Bradford[15] in dogs, and as noted in the chronic forms of Bright's disease both in children and in adults.

The *kidneys* show the lesions of an advanced primary or secondary contracted nephritis. This is true at least, where the retention uremia of Bright's disease occurs in an uncomplicated form. Frequently there is an acute diffuse glomerular nephritis implanted on the chronic condition, that is, an acute exacerbation of the chronic nephritis. This coexistence of the acute and chronic renal affections manifests itself during life in a form of uremia, which combines the characteristics of both the uremia of acute diffuse glomerular nephritis and the uremia of

renal insufficiency. Besides nephritis other diseases of the kidneys such as double polycystic kidneys, tuberculosis, etc., or obstructive processes in the urinary tract, such as urethral stricture, carcinoma of the prostate gland, bilateral calculi lodged in the ureters, etc., may be responsible for the lack of urine elimination that has been the cause for the retention uremia.

The *skin* besides showing the pallor, yellowish discoloration and slight edema, referred to under the paragraph on general condition, is at times more or less covered with a yellowish or white glistening deposit, usually called the "urea frost", because it is supposed to be derived largely from the crystallization of urea after the water of the excessive perspiration has evaporated. Erythematous eruptions and excoriations are found frequently. These may be due to dryness of the skin, rendering it vulnerable, to the restlessness of the patient and the consequent friction between the skin and the bed clothes, to scratching incident to a pruritus which may be marked, and to irritation of the crystalloids which may become deposited on the skin. Eczematoid and urticarial eruptions are frequent. The scratching and irritation of the skin are factors in favoring these lesions. The various medications administered and the retention of the urinary excretory products are also to be thought of as toxic agents for such urticarial manifestations. Hemorrhagic eruptions sometimes slight, in other instances very marked, occur towards the end of life. It may be that the blood vessels become fragile and rupture easily, or there may be a terminal bacterial invasion that is responsible. We have examined blood cultures in a number of cases, in which the hemorrhages into the skin were marked, and never obtained a positive result.

The *heart* is the seat of the marked hypertrophy and dilatation incident to a hypertension of long duration. A pericarditis is prone to develop a few days, or a few weeks before death. This is usually dry and patchy. However, it may be extensive, there may be much fibrin, the pericardium may assume a villous appearance, and at times there are small and even large amounts of fluid within the pericardial sack. The cause of the pericarditis has never been satisfactorily explained; it is probably the result of chemical irritation from the accumulation of urinary waste products in the blood and tissues; all attempts to prove that the pericarditis is of bacterial origin have failed.

The *intestinal tract* is frequently the seat of ulcers, the so-called uremic ulcers. These usually occur in the lower ileum, cæcum and colon, though they may develop in any part of the intestinal tract. I have seen one in the esophagus which caused a good deal of hematemesis (Mosenthal and Klemperer[16]), and Fishberg[17] reports a fatal perforation of an ulcer of the duodenum and a case in which the ulceration was situated so that it could be visualized by the sigmoidoscope.

The *brain* may be edematous, though as previously discussed in this chapter, this is not a constant finding. When there is an acute exacerbation of a chronic nephritis all the changes in the brain, such as the marked edema and numerous small hemorrhages described by Blackfan[9] as characteristic of the uremia of acute diffuse glomerular nephritis, may be present. The hypertension, which usually accompanies chronic Bright's disease, results in a cerebral arteriosclerosis which at times is slight and at times very marked.

In *summary* the pathology of the uremia of renal insufficiency may be regarded as extremely simple and limited, but

it becomes complex because of the conditions which lead up to it and which accompany it. Thus we must expect the morphological changes due to:

1. Uremia of renal insufficiency,
2. A primary or secondary contracted kidney,
3. An acute exacerbation of a chronic nephritis,
4. Hypertension of long standing.

Functional Pathology

The functional pathology of the uremia of renal insufficiency comprises a study of the retained urinary products and their toxic effect upon the body. This would be a simple matter if the deficient kidney action were the only factor in the situation that had to be reckoned with, but the food intake, the eliminatory functions (bowel movements, vomiting, perspiration), the compensatory processes for the acidosis and other disturbances and the medications (by mouth, by infusion, by hypodermoclyses and by rectum) are varying factors that influence the situation to such an extent as to destroy the parallel arithmetical progression in the heaping up within the body of the various substances ordinarily maintained at an approximately constant level through urinary regulation. Since the amounts of these materials that accumulate in the blood and other tissues are not constant, it must be expected that the clinical signs of intoxication will vary also. The retention of the urinary excretory products in the blood and tissues will be considered under the following heads; urea, uric acid, creatinine, amino-acids, total non-protein nitrogen, cholesterol, chlorides, sulphates, calcium and phosphates, base concentration, acidosis and alkalosis, diazo reaction.

Urea. — A rise in the urea of the blood following bilateral

nephrectomy in dogs was observed by Provost and Dumas[18] in 1821. Babington[19] (1836) found that there was an accumulation of urea in the blood in some cases of Bright's disease. These are the earliest of the researches that led to the conclusion that urea was responsible for the occurrence of uremia.

The significance of a rise in the urea of the blood involves a number of factors. If diet and mode of life remain normal and there is freedom from infectious diseases, etc., the urea in the blood becomes elevated in direct proportion to the diminution of renal excretory power. The normal amount of urea nitrogen present in the blood is usually 15 mg. per 100 c.c. or less. As renal insufficiency develops, this gradually rises until a level of 65 mg. per 100 c.c. of blood is reached, when a very marked degree of curtailment of renal function is indicated (see table 36, Chapter XII). Subsequently, as the last remnant of functioning kidney tissues is destroyed, the rise in the concentration of the blood urea nitrogen is very rapid (table 59.)

		Mg. per 100 c.c. Blood		Grams N.P.N. accumulated per day	Days elapsed
		N.P.N.	Urea N.		
Apr.	1	35	28		
	6	76	65	6	5
	16	151	124	6	10
	21	249	225	15	5
	24	426	351	45	3

TABLE 59. — Acute exacerbation of a chronic nephritis. The patient died as a result of retention uremia. The amount of non-protein nitrogen accumulated within the body during the last few days of life indicates a considerable degree of destruction of protein substance.

There are various factors to be kept in mind in the interpretation of values for blood urea. It is not only the renal

lesion of Bright's disease that will cause a rise of the blood urea. It is obvious, though often not remembered, that any obstruction of the urinary tract, urethral stricture, carcinoma, ureteral calculi, etc., will bring about a diminished elimination of urine; functional disturbances also will interfere with renal activity; thus passive congestion of the kidneys or alkalosis (see table 38, Chapter XII) may be responsible for a rise of urea in the blood. The terminal, rapid rise of the blood urea nitrogen may be in part accounted for by the protein destruction which occurs in the final stages of renal insufficiency (see table 59). A low protein diet, especially when combined with a high starch intake, often will reduce the urea nitrogen of the blood remarkably as shown in table 60.

		Mg. per 100 c.c. Blood		Per cent. urea N. of N.P.N.
		N.P.N.	Urea N.	
Oct.	8	125	99	79
	14	145	126	87
	21	123	103	84
	29	66	49	74
Nov.	16	95	63	66
	23	79	55	70
	31	41	30	73
Dec.	6	32	23	72

TABLE 60. — A case of chronic nephritis (secondary contracted kidney) with marked impairment of renal function. There are no signs or symptoms of uremia, whether the N.P.N. and the urea in the blood are at a high or a low level. When the N.P.N. of the blood is reduced by diet, the $\frac{\text{urea N.}}{\text{N.P.N.}}$ ratio remains high indicating that an impairment of renal function persists in spite of the lowered blood chemistry.

It is of interest to note the level of the urea nitrogen in the blood and tissues (muscle) in retention uremia and to study the relation of this substance to the other non-protein nitrogenous constituents. Tables 61 and 62 show that in the terminal stages of the uremia of renal insufficiency there is a marked

rise in the blood of urea, creatine, creatinine and residue nitrogen, while in the muscular tissue only the urea and the residue nitrogen show distinct elevations; the uric acid and polypeptide nitrogen in the blood and the creatinine in the

Values in Mg. per 100 c.c. of Blood

	Normal	Cases of Marked Renal Insufficiency							
N.P.N.	28.6	181	170	223	146	207	138	197	175
Urea N.	12.2	147	134	132	110	164	89	157	147
Uric acid	1.8	2.8	2.7	6.2	4.8	4.1	4.4	5.0	5.0
Creatine	4.2	9.4	9.2	17.8	9.3	14.9	10.2	29.0	15.5
Creatinine	1.3	9.3	12.9	21.3	8.5	8.1	12.7	18.5	7.7
Amino-acid N	7.9	7.0	4.9	11.8	6.6	9.7	8.0	10.0	9.8
Polypeptide N	1.9	0.5	7.6	1.7	0.3	2.8	4.9	2.8	1.7
Residue N.	4.7	18.6	14.5	60.8	20.8	20.6	26.1	7.5	6.2

TABLE 61. — The non-protein nitrogenous constituents of the blood in cases with marked renal insufficiency and retention uremia. The normal figures are average determinations in a series carried out by the same technique as used in obtaining the results in the cases with renal insufficiency.

Values in Mg. per 100 c.c. of Muscle

	Maximum	Minimum	Average	
			Uremia	Normal
N.P.N.	657	301	434	166
Urea N.	258	123	181	13
Creatine	466	287	362	350
Creatinine	25	10	15	5
Amino-acid N. . . .	39	22	28	32
Residue N..	292	19	103	7

TABLE 62. — The non-protein nitrogenous constituents of muscle in cases succumbing to the uremia of renal insufficiency. The most noteworthy increase, as compared to the normal, is in the urea and residue nitrogen.

muscle show slight increases, while the animo-acid nitrogen remains comparatively constant in both blood and muscle.

The disproportionate elevation of the blood urea nitrogen

may be resorted to as a test for renal function because it is found (Mosenthal and Hiller[20]) that while the percentage of the urea nitrogen of the total non-protein nitrogen in the blood in the presence of normal renal function is 40 to 50 per cent., when kidney activity is curtailed, this rises to 80 or even 90 per cent. This holds true as an index for renal function whether the blood urea nitrogen is high, 126 mg. per 100 c.c., table 60, or reduced by diet, 23 mg. per 100 c.c., table 60. On the other hand, when the urea nitrogen of the blood drops because there is improvement in renal function, the percentage of the urea nitrogen of the total non-protein nitrogen again assumes a normal level (see table 63).

	Mg. per 100 c.c. Blood		Per cent. urea N. of N.P.N.
	N.P.N.	Urea N.	
Oct. 27	60	45	75
Nov. 1	57	36	63
3	49	27	55
30	32	22	69
Dec. 6	19	12	63
8	14	9	64
13	16	9	56
20	18	8	44

TABLE 63. — The non-protein nitrogen and urea nitrogen of the blood in a case of acute nephritis. These values are high in the blood at first and then return to normal. The $\frac{\text{urea N.}}{\text{N.P.N.}}$ ratio is a finer index of renal function than the actual amounts of these substances as the kidney activity can only be regarded as normal when the urea nitrogen constitutes about 50 per cent. or less of the total non-protein nitrogen in the blood.

The amount of blood urea nitrogen existing in the presence of the uremia of renal insufficiency varies a great deal. The figure of 351 mg. per 100 c.c. given in table 59 is an extremely high one, and the values of 89 to 157 (table 61) are the more

usual figures. Although a level of 65 mg. per 100 c.c. indicates that the activity of the kidneys is very much diminished, no symptoms arise from such an accumulation of urea in the blood. In fact the urea nitrogen may be at levels of 100 to 125 mg. per 100 c.c. without causing any subjective disturbances.

Several experiments have been made to determine the effect of an augmented urea in the blood and in the tissues. Hewlett, Gilbert and Wickett[21] ingested large amounts of urea within a brief period and were able to raise their blood urea nitrogen as high as 111.4 mg. per 100 c.c. They found that this resulted in symptoms comparable to those characteristic of retention uremia. There developed headache, dizziness, apathy, drowsiness, weakness and fatigue. These disturbances appeared when the blood urea nitrogen rose above 68.2 mg. per 100 c.c. and ceased when it fell below this level. However, as noted in the preceding paragraph, such a concentration of urea may exist in the blood without producing any symptoms whatsoever. Probably the rapidity with which the urea was introduced into the blood and presumably into the tissues brought on the malaise, fatigue, etc., noted by Hewlett and his coworkers. A large quantity of any crystalloid material would disturb the osmotic relations under these circumstances, whereas if such substances accumulated more slowly, compensatory adjustments would be made, and the appearance of any sequalæ would be prevented.

More recently Streicher[22] injected large amounts of urea intravenously into dogs and found that there developed muscular irritability, acidosis, vomiting, diarrhea, convulsions, Cheyne-Stokes breathing, coma and death. The blood urea rose enormously and very rapidly, reaching a level of 700 mg. per 100 c.c. There were certain secondary features that accompanied the retention of urea; among these were a rise in the blood

calcium and a drop in the potassium. These accompanying changes were similar to those produced by Andrews[11] when he injected hypertonic salt solutions intravenously. It is noteworthy that Andrews was able also to induce symptoms resembling those of uremia in man. The explanation would be that it is the disturbance in the osmotic equilibrium that reproduces the picture of uremia rather than the toxic effect of one particular substance.

The blood urea, as it rises progressively in direct proportion to the diminution of renal function in Bright's disease, should not be regarded as a sign of retention uremia but rather as a sign of impaired kidney function. It is a signal of impending danger but nothing more than that. When the amount of urea, measured as urea nitrogen, rises above 100 mg. per cent., no untoward symptoms will result. This is worth bearing in mind when urea is resorted to as a diuretic. However, when the urea is retained in the body because of renal insufficiency, there are additional urinary excretory products which accumulate in the blood and tissues. The combined toxic effect of all these substances naturally is greater than that of the urea alone and results in retention uremia. Under these circumstances, it is often advisable to reduce the blood urea because it is to a certain extent an index of the retention of other substances, and when it is maintained at a level approximating the normal, many of the other products, ordinarily eliminated in the urine, will be controlled also.

Uric acid accumulates in the blood as renal insufficiency develops. It rises early in the disturbance, and it serves as a check for the urea determinations (table 36, Chapter XII). Its value as a measure for impairment of renal function is not absolute, since many other conditions besides diminished renal

activity may cause a rise of uric acid in the blood (see table 37, Chapter XII). The blood uric acid in the uremia of renal insufficiency is nearly always elevated (see table 60); values as high as 20 mg. per 100 c.c. have been noted. Feinblatt[23] found a rapid drop in the uric acid content of the blood in cases of Bright's disease moribund because of failure of renal function.

Creatinine. — As mentioned in Chapter XII there is some doubt as to the existence of creatinine in the blood. Whatever the material may be that is determined as creatinine, there is a distinct tendency for it to accumulate in the blood and tissues when renal insufficiency is far advanced (tables 60 and 61). According to Myers and Lough[24] an early fatal termination from the uremia of renal insufficiency may be expected if the creatinine blood figures reach a level of 5 mg. per 100 c.c., though there are instances where the patients have survived for one year (Myers and Killian[25]), and most of us have seen life occasionally prolonged beyond this period. The bad prognosis is not dependent upon the accumulation of creatinine in the blood but upon the rapidity with which the renal lesion advances. In Bright's disease this is prone to be fairly rapid, in some other conditions, such as polycystic kidneys, it may be very gradual.

Amino-acids, measured as amino-acid nitrogen, as a rule do not increase in the blood or muscle when the uremia of renal insufficiency is present (tables 60 and 61). Occasionally high values are found. Such instances are reported by Bock[26], who observed cases in which the amino-acid nitrogen rose almost to 30 mg. per 100 c.c. of blood. The amino-acids, which are retained within the body, normally are transformed to urea by the action of the liver and thus lose their chemical identity. An accumulation of amino-nitrogen within the body would,

therefore, be indicative of loss of hepatic function rather than of renal disease.

The total non-protein nitrogen of the blood and tissues rises in direct proportion to the degree of renal insufficiency. Since with deficient renal function an increasing percentage of the non-protein nitrogen is made up of urea nitrogen, it necessarily follows that the non-protein nitrogen has the same clinical significance as the urea nitrogen, and consequently reference is made to the preceding section on urea for a discussion of the total non-protein nitrogen.

Cholesterol. — It has been noted that, as the non-protein nitrogen rises in response to deficient kidney action, the cholesterol content of the blood diminishes (Epstein and Rothschild[27], Schmidt[28], Stepp[29], Henes[30]). From another point of view this same observation may be stated differently, namely, that a drop in the cholesterol content of the blood in severe chronic Bright's disease is indicative of a poor prognosis (Schmidt[28], Henes[30]). In our clinic we have often witnessed an inverse proportion in the fluctuations between the cholesterol and the urea in the blood. We have attributed these variations to compensatory osmotic processes. The conclusion reached was that, as urea and presumably other substances were retained because of the renal insufficiency, there was a tendency for the osmotic pressures to be stabilized by a lowering of the cholesterol in the blood. Peters and Van Slyke[31] believe that the anemia, starvation from vomiting and anorexia and cachexia of very severe renal insufficiency afford a perfect explanation for the production of a high fat, low cholesterol picture in the blood. Whatever the reason or reasons are for the fluctuations of the blood cholesterol accompanying marked impairment of renal function, it must be remembered that this is a symptom only, and that it

should not be regarded in any other light. Whether the changes in the cholesterol content of the blood are secondary to an elevation of the blood urea, to starvation, or to cachexia, makes no difference from the practical point of view, since treatment will have to be directed towards the amelioration of the renal insufficiency and its immediate sequelæ.

Chlorides are estimated as sodium chloride in the plasma or whole blood. The normal value is about 450 to 500 mg. per 100 c.c. of blood or plasma. Impairment of renal function brings about a diminished power of concentration of sodium chloride in the urine of patients with chronic Bright's disease and a consequent retention of this substance within the body. This diminished salt elimination is not accompanied by edema and has been called dry chloride retention by French authors of a generation ago. It is to be distinguished from the deficient excretion of salt in the urine occurring in patients with edema; in the latter the salt is retained because of some constitutional disturbance, and the kidneys are not at fault. This may explain the difference between the so-called "dry" and "wet" retention of sodium chloride.

No profound disturbance in the chloride metabolism is present until the uremic stage is reached. The sodium chloride content of the blood in retention uremia may be normal, though there is a distinct tendency for it to be low, and at times it may be elevated (tables 64 and 65). This variation, though not completely or satisfactorily explained, is due to a number of disturbances incidental to the uremia of renal insufficiency. The amount of sodium chloride excreted in the urine varies a great deal. Since the concentration is fixed, it depends upon the volume of urine eliminated. Usually the amount lost in this form of uremia is greater than the intake. A contributory fac-

tor in the depletion of the body's chlorine is the disappearance of the usual renal threshold of Ambard[32] to sodium chloride. In spite of a diminution in the plasma chlorides the urine contains these salts, thus leading to a loss of chlorine and base as well (Peters, Wakeman and Lee[33]).

Other factors that have to be considered as playing a part in the loss of the body's chlorides are disturbances in the intake of salt and vicarious elimination through a number of channels. There is nausea, loss of appetite resulting in a diminished food ingestion and frequently during stupor or coma no nourishment whatsoever is taken. Vomiting may be the means of losing chloride; however, this is not necessarily a reason for very great depletion of salt, because the vomitus in most instances of terminal nephritis contains little or no hydrochloric acid. The diet, which has been prescribed before the uremia of renal insufficiency actually becomes manifest, may play a rôle in the diminution of the chlorides in the blood and tissues. It is true that an indefinitely prolonged and very drastic restriction of salt in the food may have harmful effects when carried too far. Finally the intestines deserve some attention in the study of this problem. While the stools have not been studied a great deal in this connection, it has been shown by Peters, Wakeman and Lee[33] that, even in the absence of any diarrhea, large amounts of chlorine may be lost through this excretory channel.

It is perfectly true that an excess of sodium chloride will produce symptoms akin to those of retention uremia. The experiments of Andrews[11] have been cited already. He injected hypertonic salt solutions into animals and found that by raising the chloride content of the blood he produced hypertension, convulsions followed by coma, wet brain and suppression of

urine. However, as mentioned under urea, the effect is not specifically that of sodium chloride but of the excessive concentration within the blood and tissues of any crystalloid. On several occasions I have seen uremic symptoms such as stupor, general malaise, headache, nausea and vomiting brought on by allowing about 10 grams of salt per day to cases of chronic Bright's disease with a considerable degree of impaired renal function. While these facts deserve the most thorough consideration, they should not lead to the adoption of an inflexible therapeutic principle of dietary salt restriction.

I have found that the patients in the terminal stages of nephritis feel better and have fewer distressing symptoms, if the blood or plasma chlorides are determined at intervals and steps are taken to maintain the chloride concentration within the body at a more or less normal level (table 64), by modifying the salt intake, or in cases of vomiting, through the use of the Murphy drip, infusion, hypodermoclysis or any means that suggest themselves. A fatal termination is not prevented by this therapy, possibly its occurrence is deferred, but some symptomatic relief for intense suffering will be achieved. It is curious, but it is a fact, that in retention uremia the patient may suffer at times because of an excessive concentration of chlorides and at other times because of depletion of chlorides. There is no method of orientation except by frequently repeated determination of the blood or plasma chlorides.

The *sulphates* in the blood in cases of renal insufficiency have been studied only recently. Loeb and Benedict[34] found the normal SO_4 content in the blood serum to be 3.4 mg. per 100 c.c., while as the sequel to markedly diminished renal function it was as high as 51.4 mg. They believe that "inorganic SO_4 plays a relatively important rôle in the partition of the acid

radicals in nitrogen retention nephritis." The accumulation of sulphates within the body may, therefore, have a distinct influence in producing the symptoms of the uremia of renal insufficiency. They may act by changing the osmotic conditions and also by inducing an acidosis.

Phosphates. — The retention of phosphates occurs when renal insufficiency becomes marked. Dennis and Minot[35], as long ago as 1920, pointed out that a high phosphate content of the plasma indicated a poor prognosis. This finding has been amply substantiated since that time. Marriott and Howland[36] (1916) showed that the accumulation of phosphates in the blood might be responsible for the acidosis accompanying many cases of renal insufficiency in the terminal stage. They found an amount of phosphate as high as 22 mg. per 100 c.c. of blood (normal 1–3.5). Whereas the phosphates may contribute to the acidosis, they cannot be entirely responsible for it (Peters and Van Slyke[31]).

Low values for *carbon dioxide capacity* indicative of an acidosis almost invariably accompany high values for inorganic phosphorus, but low figures may be present in the absence of elevated phosphates in the blood (Schmitz, Rohdenburg and Myers[37]). This serves to show that an acidosis may be due to other factors besides the acid phosphates. There is one further fact worthy of note in connection with the rise of phosphates in the blood. It was demonstrated by Marriott and Howland[36] that this was accompanied by a marked reduction of *calcium* in the serum. This is due to the compensatory elimination of phosphates through the intestines. The phosphates are excreted through this channel only when combined with calcium. Marriott and Howland[36] found values of blood calcium as low as 1.5 mg. per 100 c.c. (normal 10–11) in chronic

nephritis with fatal uremia. A lowering of the blood calcium is believed to be a cause for the muscular twitching which is so frequently present in the uremia of renal insufficiency (Schmitz, Rohdenburg and Myers[37]).

Acidosis and Alkalosis. — The base concentration of the plasma is not available for determination in clinical medicine. It is, however, worth noting the results obtained by various investigators. A low serum base content is prone to develop in the uremia of renal insufficiency (Peters, Wakeman, Eisenman and Lee[38]). Because of the loss of power to form ammonia in advanced nephritis (Palmer and Henderson[39]) such patients must expend base for the excretion of acid metabolic waste products. "Consequently the base supplies of the body and among them the sodium of the blood plasma become depleted" (Peters and Van Slyke[31]). The effect of the elimination of chlorides in diminishing the base concentration of the serum has been discussed already.

In 1888 von Jaksch[40] demonstrated the existence of an acidosis in patients moribund because of renal insufficiency. An acid intoxication frequently is present in this form of uremia and often is the immediate cause of death. The signs and symptoms of acidosis are very deep, slow respirations (Kussmaul breathing), a lowered CO_2 combining power of the plasma, stupor and at times coma. The acidosis is not invariably present, and although it is the cause of death in many cases of retention uremia, this is not invariably so (Mosenthal[41]).

The relation, which the loss of chloride and the retention of phosphates and sulphates have to the production of acidosis, has been discussed already. Besides these there are certainly many other basic and acid substances, about which we know very little, that are factors in changing the acid base balance.

In addition to the actual chemical changes within the body certain other functional disturbances are influential in producing an acidosis. Vomiting, entailing a loss of starches and a deficient intake of sugar-producing foods, in other words, a carbohydrate starvation, may be responsible for a ketosis that accentuates the acidosis brought on through loss of basic material and by the retention of phosphates and sulphates.

Alkalosis is of rare occurrence in the uremia of renal insufficiency. It has been mentioned that the vomitus usually contains no hydrochloric acid; hence the most frequent cause for alkalosis is lacking. It is perfectly possible that the administration of an excess of bicarbonate of soda, or other alkali, may produce it, as in the patient with acute nephritis described in table 38, Chapter XII. I have seen one case where an extreme and prolonged (for several years) vegetarian diet resulted in anemia, prostration and an alkalosis accompanied by a marked retention of non-protein nitrogenous constituents of the blood; the case was pronounced hopeless, but the patient recovered beautifully with the help of dilute hydrochloric acid and the addition of meats, eggs and fish to his diet.

The *diazo reaction* in the blood becomes marked in direct proportion to the existing degree of renal insufficiency. Becher[42] ascribes this result to the accumulation of phenols; such an assumption is, however, not necessarily correct, since there is no proof thus far that phenols are actually present in the blood of patients succumbing to deficient renal activity (Peters and Van Slyke[31]).

Cause

It is self evident that the retention of urinary excretory products within the body is the cause for the toxic condition

which we have called the uremia of renal insufficiency. However, this does not sum up the situation completely or satisfactorily, for the question remains as to which one of the many substances, usually eliminated by the kidneys, is at fault.

It is definitely known that an acidosis is one of the factors that may be responsible for a fatal termination. The retention of acids, notably phosphates and sulphates, has been mentioned, and the depletion of basic material by the vicarious elimination of calcium in combination with phosphates through the intestinal mucous membrane and the loss of base associated with the ready chloride excretion in the urine have been described. These are the principal known elements in the situation; there may, of course, be others that have not been studied. However, even if acidosis is prevented or set aside, these patients will succumb.

We have noted how a very marked amount of urea or salt (far more than exists in human beings suffering from retention uremia) will duplicate the symptoms and signs of the uremia of renal insufficiency in experimental animals. Yet no one has offered convincing evidence that the urea, uric acid, creatinine or any other substance is the specific etiological factor. It is doubtful whether the deviation from the normal of any one crystalloid or colloid material can be blamed for this type of uremia. It is more probable that it is the summation of the toxic action of all these products that causes the uremia. It is not the individual effect of any one substance but the aggregate that is responsible for this intoxication, called retention uremia.

Foster[43] has obtained an unidentified organic base from the blood of uremic patients, which produced convulsions when injected into guinea pigs. It may be that this is the sole toxic factor to which the uremic symptoms must be accredited; on

the other hand, it may be only one of a number. The accumulation of a residual, unidentified, non-protein nitrogen fraction in the blood and muscle of uremic patients (see tables 61 and 62) suggests that there are some unknown substances, which may include the organic base of Foster, that await study and identification.

Symptoms, Signs and Clinical Course

The onset of symptoms secondary to inadequate renal function is very gradual. It is remarkable that many patients with extreme reduction in the excretory power of their kidneys feel very well and can pursue their usual activities without being in the least conscious of their impairment; the urea nitrogen frequently is at a level of 100 mg. per 100 c.c. or more in the blood without causing any malaise or discomfort. It would appear that the earliest symptoms ascribed to retention uremia, i.e., weakness, lassitude, vertigo, dyspnea and headaches, are probably due either to secondary anemia with its usual sequelæ or to the effect of a persistent hypertension resulting in cardiac weakness and cerebral arteriosclerosis.

When the actual symptoms begin, there is a progressive loss of strength which the patient feels very keenly, and he is likely to seek the advice of successive physicians in his endeavor to overcome what he considers an unwarranted infringement on his well-being. The weakness and lethargy increase gradually. There may be no further symptoms over a period of weeks or months. Undoubtedly the cachexia and secondary anemia, that are the usual accompaniment of marked renal insufficiency, are responsible to a certain degree for these early signs. Loss of appetite, nausea to a greater or lesser degree, headache, vertigo, visual disturbances and dyspnea are often added to the lassi-

tude. It is probable that the hypertension with its attendant cerebral arteriosclerosis and cardiac weakness and retinitis play a certain part in producing these effects and that the renal insufficiency cannot be blamed for them entirely.

Nausea and Vomiting. — The weakness gradually increases; loss of appetite, then nausea and finally vomiting follow. The vomiting occurs occasionally at first, then becomes more or less persistent. The vomiting takes place after eating and also at irregular intervals. It would seem that there are two causes for the vomiting; one, an irritabil ty of the stomach, the second, a central nervous system disturbance which causes retching and emesis irrespective of the food intake. The vomiting may become persistent and frequent; on the other hand, it may be intermittent, occurring only once every three or four days (table 64). It has seemed to me that it could often be controlled to a great extent if the NaCl content of the blood and the acidosis, as measured by the CO_2 combining power of the plasma, were kept at approximately normal values, which can be accomplished by the judicious use of salt and alkalis by mouth, rectum, infusion or hypodermoclysis. The patient is made decidedly more comfortable by these means, even though the chances for recovery are not enhanced.

Duration. — The weakness gradually increases, deepening progressively into stupor, coma and death. The usual interval, that elapses from the time the patient takes to his bed until exitus occurs, is four to six weeks, though there is a wide variation for this terminal period. Its duration depends largely upon the temporary success of the symptomatic treatment and also upon the rate of progress of the pathological lesion in the kidney. When the latter is extremely slow, and in fact almost imperceptible, as is the case in polycystic renal disease, there

Date	Urine		Blood mg. per 100 c.c.		CO_2 plasma	Vomiting times per day	Remarks
	Vol. c.c.	Sp.G.	Urea N.	NaCl			
Mar. 20	610	1.008	109		45	2	Prostration marked
21	740	1.010				2	
22	800	1.008				0	
23	650	1.009				0	
24	1140	1.010	85	354	71	1	
25	900	1.010				0	
26	1000	1.012				0	
27	1100	1.006	93	519	78	0	Feels stronger
28	1680	1.012		435	79	1	
29	900	1.010				0	
30	1300	1.014	82	445	63	0	
31	1500	1.011				0	Muscular twitching from this day on
Feb. 1	2200	1.010				0	
2	2000	1.007	104	435	63	0	Irrational at times from now on
3	1500	1.005				0	
4	1750	1.010				0	
5	1860	1.012	74	453	46	0	
6	580	1.012				1	Pericardial rub distinct and is intermittently present until death
7	740	1.010				0	
8	1090	1.010				0	
9	825	1.010	77	470	32	0	
10	1000	1.010				0	
11	720	1.007				1	
12	500	1.007				1	
13	630	1.010				1	
14	820	1.008				0	
15	1150	1.008	71	519	47	0	
16	800	1.010				1	
17	360	1.009				0	
18	240	1.008				0	
19	60					3	Two general convulsions
20	100					1	Two general convulsions
21							Died

TABLE 64. — Uremia of renal insufficiency in a man aged 40, the terminal stage of a secondary contracted kidney. The attempt was made to maintain the blood chlorides and the plasma CO_2 at normal levels by forcing fluid, alkalis, sodium chloride, glucose and food when indicated. In spite of this, death occurred when the oliguria became marked. The specific gravity of the urine remained low throughout. The irregular vomiting, the muscular twitchings, the pericarditis, a few convulsions prior to exitus and the terminal oliguria are typical of this form of uremia. VOL. 7. 31.

may be complete recovery from these symptoms of renal insufficiency after elimination of acidosis, cessation of vomiting, restoration of the cardiac power and an amelioration of the secondary anemia have been accomplished. In the retention uremia of chronic Bright's disease, however, the condition usually is progressive, and the resumption of ambulatory activities is scarcely ever attained. Death, as mentioned above, usually comes on within six weeks after the patient is prostrated to such an extent that he remains in bed, though his illness may be more lingering, and the period of invalidism may last as long as six months.

Nervous System. — Foster[43] gives a description of the symptoms and signs of uncomplicated renal insufficiency as they developed in three patients whose only functioning kidney had been removed during emergency operations. "In none of these was there the slightest irritability of the motor nervous system or impairment of the psychic function until the last days of life. All alike experienced first, weakness, slight vertigo and mental dullness; then a tendency to sleep which lapsed into coma with death on the ninth or eleventh day after operation." This is the same clinical picture that is witnessed in laboratory animals when both kidneys are extirpated. In patients dying as the result of gradually advancing renal insufficiency, whether it be due to Bright's disease, obstruction of the urethra, bilateral involvement of the ureters, paralysis of the bladder or other causes, there are usually additional symptoms referable to the nervous system. The most constant of these is an intermittent fine muscular twitching, which is most frequently noted in the forearms, hands, fingers and face, though it may be found in any of the voluntary muscles. Probably it would be demonstrated with equal frequency in the non-exposed parts of a

patient, if we would take the trouble to search for this disturbance. I have seen it often in the pectoral muscles, while a physical examination of the heart was carried out. If the patient's hand is held at the bedside, a tapping of individual fingers will often disclose the existence of this muscular activity. The study of any stuporous individual for such twitchings often will lead to the correct diagnosis of the cause of the semi-

Date	Fluid Metabolism in c.c.				Blood Chemistry, Mg. per 100 C.C.							
	Fluid by Mouth	Infusion or Hypodermoclysis	Total Intake	Total Output Urine	Urea N.	Uric Acid	Creatinine	NaCl	Ca	Phosphates	CO_2 Plasma	Blood Pressure
Jan. 27					77		12				83	234/16
28												224/14
29											66	224/15
30	2970	1000	3970	660	100	9	12	396	9.4	6.3	58	
31	3870	500	4370	960	94							
Feb. 1	1770	500	2270	900				396			50	210/13
2	1500	600	2100	960	124							200/12
3	1050	600	1650	480							50	
4	2280	1000	3280	480	117	9		435				220/13
5	2040	1000	3040	945					9.5	6.5		218/13
6		1100	1100	780	147	12	13					
7	Died											

TABLE 65. — Uremia of renal insufficiency in a man aged 37. This case illustrates the following points: oliguria in spite of a high fluid intake; there were marked muscular twitchings, although the blood calcium was not diminished; there was no acidosis. The blood pressure was high to the end; death was apparently due to the retention of urinary excretory products in spite of the fact that there was no noteworthy disturbance in the acid base balance and that there was no cardiac insufficiency.

conscious state; I know of one case where the diagnosis of carcinoma of the urethra was made when this phenomenon was observed. Such muscular twitchings have been attributed to a depression in the calcium of the blood to a level below 7 mg. per 100 c.c. (Schmitz, Rohdenburg and Myers[37]). However they may be present with normal values for blood calcium (see table 65).

Furthermore, there are other symptoms referable to the

central nervous system. The vomiting which occurs as the result of cerebral irritation has been alluded to already. Isolated convulsive seizures, especially a day or two before death, are often in evidence (see table 64). A series of such convulsions is sometimes present as in the type of intoxication accompanying acute nephritis, but it is extremely rare in retention uremia. The patients affected by marked renal insufficiency are prone to be irrational, talk at random, be noisy and sometimes are so restless that forcible restraint becomes necessary.

These and other affections ascribable to the central nervous system probably are not the result of the accumulation of urinary excretory products in the blood but are more likely to be the effect of the concomitant cerebral arteriosclerosis, vasospasm or edema. However, they are of such frequent occurrence that they have to be regarded as part of the clinical picture.

Blood Pressure. — The blood pressure at the onset of retention uremia is characteristic of that previously existing in the patient, that is, the blood pressure is usually elevated, though it may approach the average normal level. A retention of renal excretory products in itself, as discussed in Chapter XV, will bring about a moderate rise in blood pressure. As the condition becomes more serious and the fatal termination approaches, the blood pressure frequently, though not invariably, drops. Both the systolic and the diastolic pressures are found to be lower at this time. It is very noticeable that the patients are usually just as comfortable with the lower blood pressure as they were with the arterial tension at a higher level. The cause for the diminution in the blood pressure level is to be sought in a loss of power of all the organs which contribute towards the maintenance of the arterial tension. It is probably

due to the weakening of the muscles of the heart and the arteries as well. As a rule, death may be expected to occur within two to four weeks after the blood pressure becomes lowered. Sudden rises of blood pressure, such as are witnessed in acute nephritis or in uncomplicated essential hypertension, are scarcely ever witnessed in the terminal stages of renal insufficiency.

The *heart* is the seat of the hypertrophy and dilatation incidental to the existence of a prolonged hypertension. There frequently is a certain amount of myocardial insufficiency. The pericarditis, usually fibrinous, which is such a bad prognostic sign, has been discussed already in the section on morphological pathology.

The *blood count* indicates a marked secondary anemia. The hemoglobin index may be either positive or negative. For details in regard to the hematological findings accompanying renal insufficiency reference is made to Chapter XIV.

The non-protein nitrogenous constituents of the blood, except the amino-acids, usually are all considerably above the normal levels (see table 61). The CO_2 combining power of the plasma is generally, though not always, below normal indicating an acidosis; the phosphates are prone to be high, and the calcium content of the blood to be low; the chlorides have a tendency to be diminished; the sulphates are increased; other substances in the blood usually are not determined in clinical studies. Sometimes for no apparent reason, at others because of suitable treatment, there is a maintenance of the substances concerned in the production of an acidosis (NaCl, Ca, CO_2 combining power, phosphates) at a more or less normal level (see tables 64 and 65), and yet the symptoms and signs, except for the absence of Kussmaul

breathing and the delayed advent of coma, remain much the same.

The *intestines* (see morphological pathology) may be the seat of the so-called uremic ulcers. These may occur anywhere in the digestive tract from the pharynx to the rectum. They are often responsible for the presence of a considerable amount of blood in the vomitus and in the stools. The diarrhea, which supposedly represents an attempt at vicarious excretion of the retained urinary excretory substances, and which has been stressed in some of the older textbooks of medicine, usually is conspicuous by its absence.

Skin. — A marked pallor with an icteric tint of the skin and sclera, incident to the secondary anemia and a low grade hemolysis, is characteristic. An excessive degree of perspiration, which on drying leaves a yellowish, flaky, glistening deposit known as "urea frost" may be found during the last few days of life. There may be hemorrhagic eruptions, possibly indicative of terminal infections, erythematous eruptions and skin infections because of the rubbing of the skin by the restless patient on the bed clothes and at times allergic skin manifestations.

The *kidneys* and *urine* are the keystone upon which the advent and progress of the uremia of renal insufficiency depend and naturally will be watched with intense interest. The progressively diminished activity of the kidneys is noted first when the blood chemistry is maintained at a normal level through polyuria. When this compensatory process fails, the blood urea nitrogen and other substances begin to accumulate and give warning of impending danger. There are two influences that may accelerate the course of events by influencing renal activity adversely; these are cardiac insufficiency and an acute exacerbation of the chronic nephritis.

Albumin may be present in large amounts or as mere traces in the urine. This depends upon the lesion in the kidneys and in itself has no bearing upon the adequacy of renal function. An albuminuria may be increased through the presence of passive congestion of the kidney or by an acute exacerbation of the chronic nephritis.

Casts are evident in kind and numbers according to the existing type of nephritis. The appearance of the "renal failure casts" has been described in Chapter XI.

Red blood cells usually are absent in the urine in cases of chronic nephritis. Some of them may be found, but their presence in any significant numbers points to the complication of the uremia by passive congestion or an acute inflammatory process in the kidney.

The reaction of the urine often is alkaline, probably due to the excessive elimination of basic material, though in many cases the reaction is distinctly acid throughout the course of the uremia. This question deserves considerably more attention from the clinical side than it has received thus far.

The volume of urine becomes progressively and inevitably less, in spite of sufficient fluid intake (tables 64 and 65), and urinary secretion may even cease entirely (figure 7, Chapter XII). It is the development of oliguria that is responsible for the marked curtailment of kidney function and the fatal termination of the uremia of renal insufficiency.

The specific gravity of the urine is constantly in the neighborhood of 1.010 (table 64). There are certain variations that have a distinct significance. Where in the presence of a high blood urea the specific gravity is below 1.010, there must be a further diminution in the power of the kidney to concentrate which may be temporary or permanent. In the agonal stage, or

when passive congestion of the kidney develops, the specific gravity may rise to about 1.014, though this does not necessarily occur (table 64, and figure 7, Chapter XII). The significance of this change in urinary concentration has been discussed for many years, and its meaning is not fully understood at the present time. It has been shown (Mosenthal[44]) that when a maximal degree of renal insufficiency exists, the kidney opposes an insuperable barrier to all stimuli that call for a more concentrated urine; if, however, there is a factor of safety still existing within the kidney, then the added demand for a higher specific gravity, whether it be diminished fluid intake, vomiting or diarrhea, or deficient cardiac power and passive renal congestion, will cause the specific gravity to rise. In estimating renal function by the specific gravity of the urine not only the amount of active kidney parenchyma must be considered, but the type and intensity of the stimuli for urine formation must be taken into account as well. The matter cannot be judged according to rule of thumb by a simple formula, but it must be interpreted by giving the existing morphological and functional pathology, not only of the kidneys but of the whole body, due consideration.

Treatment

The treatment of the uremia of renal insufficiency must necessarily be symptomatic, since it is impossible to change the structure of the primary or secondary contracted kidney, whose diminished amount of active tissue is responsible for the condition.

The most important consideration is to *maintain as large a volume of urine* as possible. There should be a fluid intake of

3,000 c.c. a day. This, as previously shown, is the maximal quantity which the kidneys can use to advantage in eliminating solids. The use of any diuretics, besides water, with the possible exception of digitalis at times, is of no value and is contra-indicated. The high amounts of urea and other crystalloids in the blood provide a maximal diuretic stimulus without the addition of drugs. Digitalis often is effective, because the heart frequently does not maintain a normal circulation. The cachexia, anemia and hypertension, all contribute to this cardiac weakness. Even when there is no apparent lag in the heart action it is often worth while to administer digitalis. The therapeutic test does no harm and may improve matters a great deal.

Fluid Intake. — The form in which the fluid is taken makes very little difference. Water and fruit juices are recommended by every one; tea and coffee do no harm and are generally forbidden because of tradition; the contentment brought on by indulgence in a favorite beverage is often a great comfort; alcohol in moderate amounts is very valuable as a food and as a sedative, and there is no proof that, in sensible amounts, it is at all harmful; mineral waters must be used according to the acid base balance in the blood; ginger ale and other "soft" drinks may be given without stint.

Fluid Administration. — Fluid should be given by mouth to the exclusion of other methods of administration whenever possible. The use of a permanently retained gavage tube often solves the problem of feeding semi-conscious or comatose patients. When there is much vomiting, recourse must be made to infusions, hypodermoclyses, retention enemata or the Murphy drip. The kind of fluid to be used depends upon the findings in the blood; a low blood chloride calls for saline solutions; an

acidosis or need for food is an indication for 10 or 20 per cent. glucose solutions. These may be given separately, or the glucose and salt may be combined. When the acidosis is marked, 5 per cent. bicarbonate of soda may be used; care must be taken that the acidosis is not over-corrected and an alkalosis produced. About 20 grams of bicarbonate of soda a day usually is more than an ample amount, except for brief periods of a day or two.

The diet, aside from the aspect of fluid administration, must be adjusted in regard to the amount of sodium chloride, the quantity of protein and the total calories. Frequently the nausea and vomiting prevent the administration of the most suitable foods, and compromises have to be made between what is ideal and what is feasible.

Salt should never be given in large amounts. About 5 grams a day is all that is required when the blood chlorides are at a low level; when the chloride content of the blood is normal or high, a salt-free diet is advisable.

If it is desired to diminish the urea concentration in the blood, a low protein, high starch and fat diet is indicated. Such a diet is given in the list on the opposite page.

It should be remembered that by reducing the blood urea the other products that have accumulated in the blood follow suit and are more or less controlled. The level of the blood urea nitrogen may, therefore, be used as an index of the need for a low protein diet. It has been mentioned in the section on renal function that it is not advisable to be too enthusiastic about protein restriction and that a rigid curtailment, as outlined in the present diet, is indicated only when the blood urea nitrogen reaches a level of 65 mg. per 100 c.c. or more.

The *control of acidosis* should be guided by the CO_2 com-

Low Protein Diet

Breakfast:

Sherry or port wine, 30 c.c.
Baked apple, apple sauce, orange juice, grapefruit juice, stewed prunes.
Hominy-cornstarch cereal.*
Cream 30 c.c.
Arrow-root biscuits.
Honey, sugar, butter, jams, jellies.

Dinner:

Sherry or port wine, 30 c.c.
Potato, baked or mashed.
String beans, cabbage, carrots, lettuce, onions, tomatoes, cucumber, pickles.
Fruit cornstarch or fruit tapioca pudding.
Arrow-root biscuits.
Olive oil, lemon juice, vinegar.
Honey, sugar, butter, jams, jellies.

Supper:

Same as dinner.

The amount of salt allowed must be determined for each patient.

Nitrogen Content of Foods used in Low Protein Diet

(For protein content multiply nitrogen by 6.25)

Food	*Percentage of nitrogen*
Cereal	
Cream	.41
"Hominy-cornstarch"	.13
Fruit	
Baked apple	.04
Orange	.16
Stewed prunes	.14
Vegetables	
Cabbage	.16
Carrots	.10
Lettuce	.24
Onions	.17
Cucumber pickle	.10
Baked potato	.48
Mashed potato	.40
String beans	.23
Tomato	.23
Desserts	
Fruit cornstarch or Tapioca pudding	.02 to .07

The arrow-root biscuits, sugar, honey, jam, jellies, butter, olive oil, contain negligible amounts of nitrogen or protein.

*2/3 hominy, 1/3 cornstarch, mixed in cereal or flour form, before adding water and boiling.

bining power of the plasma. When this is low (below 40 volumes per cent.), the administration of alkali by mouth, vein or rectum is indicated. Bicarbonate of soda is the usual medication. Care must be taken that the condition is not overcorrected, and that an alkalosis is not produced. Ten to twenty grams, or two to six drachms, of the bicarbonate should not be exceeded on any one day. The drug should be discontinued when the CO_2 combining power of the plasma reaches a level of between 50 and 60 volumes per cent. The quantity of basic material lost and the amount of acid substances accumulated within the body because of renal insufficiency in a 24 hour period is comparatively small; consequently the measures for its correction within a short period of time should not be too drastic.

The steps, previously advocated for the control of the urea and the chlorides in the blood and tissues, will serve also to stabilize the acid base balance within the body. The low protein, high starch diet and adjustment of the salt intake all work towards this end. However, it is best to employ these therapeutic means according to the indications given by the quantity of urea and sodium chloride of the blood and to make no specific effort thereby to control the acidosis. When the acidosis gets out of hand, the use of alkali, as mentioned at the beginning of this section, is the simplest and readiest means for controlling the disturbance.

It must be kept in mind that if the acidosis is regulated on any one day, it may recur within a brief period, because the renal insufficiency will cause a constant accumulation of the acid substances which ordinarily would be eliminated.

Sedatives may be necessary for the control of restlessness or delirium. The barbituric acid compounds are rarely of much

value. Chloral, 2 to 4 grams (30 to 60 grains), by mouth or rectum, often has splendid results; at other times it may increase the nervous irritability. I have never used paraldehyde because of its disagreeable odor which would be an added annoyance to the patient and his visitors during a rather prolonged and serious illness. Morphine sulphate, 15 mgm. (grains ¼), with or without hyoscine hydrobromide, 0.6 mgm. (gr. 1/100), repeated as necessary, usually accomplishes the desired result. The bad effects upon the kidney action, about which there have been so many warnings, do not materialize.

The *intestines* may be kept active by saline cathartics, compound rhubarb pills or any desired medication provided it does not contain calomel or other forms of mercury. The oily or bulky medicines for intestinal control usually are not satisfactory, because they result in distention and large, putrid stools that complicate the management of the case. In many instances enemata, or better still rectal irrigations, serve to keep the lower intestines in proper shape for rectal absorption of food and fluid and to maintain the whole intestinal tract free from distention and accumulation of fecal material with the least discomfort to the patient.

The *heart*, as mentioned before, may fail to maintain an adequate circulation. Anemia and cachexia have starved the cardiac muscle, and the previous hypertension has put a great strain upon it. Consequently the use of digitalis is often indicated.

Anemia usually is present and is marked. It is of doubtful advisability to pay much attention to the anemia during an attack of uremia brought on by renal insufficiency in chronic Bright's disease, because a high protein diet and iron medication

are contraindicated and moreover require time to become effective, and furthermore so drastic a measure as blood transfusion, while a help for the anemia, fails to prevent the fatal outcome of the uremia.

Accessory Elimination. — The measures designed to relieve the body of toxic products are numerous but have been largely abandoned as ineffective in the treatment of the uremia of renal insufficiency. Bleeding usually is contraindicated because of the anemia; if the hemoglobin is 80 per cent. or more, it may be tried. Rectal irrigations are of some value; they cleanse the intestines, they stimulate through heat, they provide fluid for absorption, and they may remove some toxic products. Hot packs, electric light cabinets and other procedures designed to promote sweating have been largely abandoned as being too debilitating and as being sterile of results; recently Allen[45] has given prolonged sweats by means of a specially constructed heat chamber in the early stages of uremia of renal insufficiency and has claimed good results.

Occurrence of Uremia in the Various Forms of Nephritis

The nomenclature employed here to designate the different types of uremia are self-explanatory in this connection.

The uremia of cerebral arteriosclerosis may develop as a sequel to a prolonged hypertension whenever this occurs in Bright's disease. This is usual in the course of

Essential hypertension,

Primary contracted kidney,

Chronic diffuse glomerular nephritis,

Secondary contracted kidney.

The uremia of acute diffuse glomerular nephritis, sthenic,

convulsive, or epileptiform uremia, accompanies acute diffuse glomerular nephritis or an acute exacerbation occurring in the course of a chronic nephritis.

The uremia of renal insufficiency, asthenic uremia, or retention uremia, is the sequel of a prolonged and marked degree of diminished excretory activity of the kidneys from any cause whatsoever. The forms of Bright's disease in which this occurs are the subacute diffuse glomerular nephritis, the primary and the secondary contracted kidneys, and the anuric form of tubular nephritis (bichloride of mercury poisoning).

The forms of nephritis in which uremia does not occur are: the focal glomerular nephritides, the tubular nephritides with the exception of the anuric type (bichloride of mercury poisoning) and the chronic diffuse glomerular nephritis, that is, the stage of chronic nephritis in which renal function is still adequate, before the kidney becomes contracted by fibrous tissue formation.

Bibliography

1. Cohnheim, J.: Vorlesungen über Allgemeine Pathologie, August Hirschwald, Berlin, 1882.
2. Ascoli, G.: Vorlesungen ueber Urämie, Fischer, Jena, 1903.
3. Peabody, G.: Relations between arterial disease and visceral changes, Trans. Assoc. Am. Phys., **6**: 170, 1891.
4. Osler, W.: Transient attacks of aphasia and paralysis in states of high blood pressure and arteriosclerosis, Canad. Med. Assoc. Jour., **1**: 919, 1911.
5. Pal, J.: Die Gefässkrisen, S. Hirzel, Leipzig, 1905.
6. Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive encephalopathy, Arch. Int. Med., **41**: 264, 1928.
7. Mosenthal, H. O.: Essential hypertension, Med. Clin. No. America, **1**: 101, 1917.
8. Traube,: Eine Hypothese ueber den Zusammenhang in welchem die sogenanten urämischen Anfälle zur Erkrankung der Niere stehen, Allgemeine med. Centralzeitung, **30**: 817, 1861.

9. Blackfan, K. D.: Acute nephritis in children, with special reference to the treatment of uremia, Bull. Johns Hopkins Hosp., **39**: 69, 1926.
10. Cushing, H.: Concerning a definite regulatory mechanism of the vaso-motor centre which controls blood pressure during cerebral compression, Bull. Johns Hopkins Hosp., **12**: 290, 1901.
11. Andrews, E.: Experimental uræmia, Arch. Int. Med., **40**: 548, 1927.
12. Calvin, J. K.: Uremia in children, Med. Clin. No. America, **13**: 1211, 1931.
13. Kennedy, F. and Wortis, S. B.: Modern treatment of increased intracranial pressure, Jour. Am. Med. Assoc., **96**: 1285, 1931.
14. Ashe, B.: The hemoglobin percentage and the red blood cell count in Bright's disease, myocardial insufficiency and hypertension, Arch. Int. Med., **44**: 506, 1929.
15. Bradford, J. R.: The results following partial nephrectomy and the influence of the kidney on metabolism, Jour. Physiol., **23**: 415, 1899.
16. Mosenthal, H. O. and Klemperer, P.: Subacute nephritis, Med. Clin. No. America, **10**: 907, 1927.
17. Fishberg, A. M.: Hypertension and nephritis, Lea and Febiger, New York, 1930.
18. Provost and Dumas, 1821, quoted by Foster, N. B. in Cecil's Text Book of Medicine, p. 923, W. B. Saunders & Co., Phila., 1930.
19. Babington, J. P., cited by Bright, R.: Cases and observations illustrative of renal disease. Guy's Hosp. Med. Reports, London, **1**: 360, 1836.
20. Mosenthal, H. O. and Hiller, A.: The relation of the non-protein nitrogen to the urea nitrogen of the blood, Jour. Urol., **1**: 75, 1917.
21. Hewlett, A. W., Gilbert, G. O. and Wickett, A. D.: The toxic effects of urea on normal individuals, Arch. Int. Med., **18**: 636, 1916.
22. Streicher, M. H.: Experimental uremia, uremic enteritis, Arch. Int. Med., **42**: 835, 1928.
23. Feinblatt, H. M.: Uricacidemia. Based on a study of 1500 blood chemical analyses, Arch. Int. Med., **31**: 758, 1923; An analysis of twenty-nine cases of uremia, N. Y. Med. Jour. and Med. Record, **67**: 737, 1923.
24. Myers, V. C. and Lough, W.: The creatinine of the blood in nephritis — its diagnostic value, Arch. Int. Med., **17**: 536, 1915.
25. Myers V. C. and Killian, J. A.: The prognostic value of creatinine of the blood in nephritis, Am. Jour. Med. Sc., **157**: 674, 1919.

26. Bock, J. C.: The amino acid nitrogen content of the blood of various species, Jour. Biol. Chem., **29**: 191, 1917.
27. Epstein, A. A. and Rothschild, M. A.: The lipoids of the blood in renal conditions, with special reference to the cholesterol content, Am. Jour. Physiol., **42**: 586, 1916.
28. Schmidt, H. B.: A clinical study of cholesterinemia in patients with nitrogen retention, a preliminary report, Ann. Clin. Med., **1**: 66, 1922.
29. Stepp, W.: Ueber den Cholesteringehalt des Blutserums bei Krankheiten, Münch. med. Woch., **65**: 781, 1918.
30. Henes, E. Jr.: The prognostic value of cholesterinemia in chronic nephritis, Arch. Int. Med., **25**: 411, 1920.
31. Peters, J. P. and Van Slyke, D. D.: Quantitative clinical chemistry Volume I, Interpretations, Williams and Wilkins, Baltimore, 1931.
32. Ambard, L.: Physiologie des Reins, Masson & Cie., Paris, 1919.
33. Peters, J. P., Wakeman, A. M. and Lee, C.: Total acid-base equilibrium of plasma in health and disease. XI. Hypochloremia and total salt deficiency in nephritis, Jour. Clin. Invest. **6**: 551, 1929.
34. Loeb, R. F. and Benedict, E. M.: Inorganic sulphates in human blood, Jour. Clin. Invest., **4**: 33, 1927.
35. Denis, W. and Minot, A. S.: A study of phosphate retention from the standpoint of blood analysis, Arch. Int. Med., **26**: 99, 1920.
36. Marriott, W. McK. and Howland, J.: Phosphate retention as a factor in the production of acidosis in nephritis, Arch. Int. Med., **18**: 708, 1916.
37. Schmitz, H. W., Rohdenburg, B. S. and Myers, V. C.: The inorganic phosphorus and calcium of the blood in nephritis, Arch. Int. Med., **37**: 233, 1926.
38. Peters, J. P., Wakeman, A. M., Eisenman, A. J. and Lee, C.: Total acid-base equilibrium of plasma in health and disease. X. The acidosis of nephritis, Jour. Clin. Invest. **6**: 517, 1929.
39. Palmer, W. W. and Henderson, L. J.: A study of several factors of acid excretion in nephritis, Arch. Int. Med., **16**: 109, 1915.
40. von Jaksch, R.: Ueber die Alkalescenz des Blutes bei Krankheiten, Zeit. f. klin. Med., **13**: 150, 1888.
41. Mosenthal, H. O.: Metabolism in nephritis, in Endocrinology and Metabolism, D. Appleton & Co., New York, 1922.
42. Becher, E.: Über einige neue Blutbefunde und Reaktionen bei echter Urämie, Klin. Woch., **4**: 924, 1925.
43. Foster, N. B.: Uremia, Jour. Am. Med. Assoc., **76**: 281, 1921.

44. Mosenthal, H. O.: Renal function as measured by the elimination of fluids, salt and nitrogen, and the specific gravity of the urine, Arch. Int. Med., **16**: 733, 1915.

45. Allen, F. M.: Observations on sweating, New England Jour. Med., **201**: 806, 1929.

CHAPTER XVII

SUMMARY

The Grouping of Bright's Disease

This final chapter is not a summary, in the sense that it is an epitome of, and a ready reference for, the details that have been printed in this book. The purpose of this last chapter is to answer as fully as possible the ever recurring question, of both practitioners and students; "What is your classification of nephritis?"

From the author's point of view, this query has been answered to the best of his ability in Chapter X. Here it was stated that Bright's disease is not an entity, but that it is composed of several processes developing more or less independently and to varying degrees in different patients. These "problems" in Bright's disease are:

1. Pathology of the kidney and other tissues,
2. Renal function,
3. Edema,
4. Blood pressure,
5. Anemia,
6. Uremia.

Two years' further experience, since this volume was begun, has not altered my conviction that the most complete analysis of Bright's disease and the most satisfactory guide for its treatment are obtained by ferreting out independently each of the above six deviations from normal anatomy and function

and according individual study and attention to each one. This method of analyzing and diagnosing cases of Bright's disease diverges widely from that advocated by most authors. The morphological pathology of the kidneys usually is made the hub of the wheel about which the signs and symptoms of the disease are made to revolve. Text books state emphatically that Bright's disease is a constitutional affection, one that is not confined to the kidneys, and yet, in spite of this expressed belief, the anatomical changes in the renal parenchyma are made the pivotal point in the study of nephritis. This has some justification, if the term nephritis is retained. It is because of the very diverse character of the anatomical and functional disturbances in this group of affections and their widespread distribution within the body that "nephritis" is a misnomer and that the collective term "Bright's disease" is much more satisfactory.

Even if these are the views which have been advocated in the present volume, the whole plan will perhaps be better understood if the various forms of Bright's disease are briefly analyzed by grouping the functional and anatomical changes about the renal lesions with the exception of hypertensive disease, in which the symptoms and signs are dependent solely on the increased blood pressure.

Grouping of Bright's Disease

Attention is called to the fact that in this book the term nephritis is reserved to designate the pathological changes which occur in the kidneys, whereas the name Bright's disease is applied to the various clinical pictures customarily grouped about these renal lesions.

I. Essential hypertension

II. Glomerular nephritis
    1. Diffuse glomerular nephritis
        (*a*) Acute diffuse glomerular nephritis
        (*b*) Subacute diffuse glomerular nephritis
        (*c*) Chronic diffuse glomerular nephritis
    2. Focal glomerular nephritis
        (*a*) Focal infectious glomerular nephritis
        (*b*) Focal embolic glomerular nephritis
III. Tubular nephritis
    1. Albuminuric tubular nephritis
    2. Anuric tubular nephritis
    3. Edematous tubular nephritis
    4. Hypertensive and convulsive tubular nephritis
IV. Arterial nephritis
    1. Sclerosis of the arteries and arterioles (benign nephrosclerosis)
    2. Arteriolar necrosis (malignant sclerosis)

Disturbances Associated with Essential Hypertension

Essential hypertension, the "hyperpiesis" of Sir Clifford Allbutt, the "hypertensive cardiovascular disease" of Theodore Janeway, is a disease of unknown etiology, characterized by a persistent and progressive rise of both the systolic and the diastolic blood pressure.

Pathology

Arteriosclerosis is usually present to a greater or lesser extent throughout the body. The organs in which the most important changes take place are the heart, the brain and the kidneys.

Heart. — The heart becomes hypertrophied; the hypertrophy is followed by dilatation and finally by myocardial insufficiency. Sclerosis of the coronary arteries is common, causes angina pectoris and, through degeneration of the cardiac muscle, plays a part in the production of myocardial insufficiency. Sixty per cent. of the deaths occurring in the course of essential hypertension are due to heart disease.

Brain. — Cerebral arteriosclerosis and arteriolosclerosis is often marked, may result in cerebral hemorrhage or thrombosis and, if it is extensive, will bring about encephalomalacia. Twenty per cent. of the deaths occurring in the course of essential hypertension are due to involvement of the cerebral blood vessels.

Retina. — There is nearly always arteriosclerosis of the retinal vessels; various degenerative changes are common; the form of retinitis known as "albuminuric retinitis" and the lesions resulting from an increased intracranial pressure often are marked.

Kidneys. — A certain degree of sclerosis of the arteries and of the arterioles is present practically always. This process rarely advances beyond the limits of a moderate arteriosclerotic nephritis, though the disease may progress more rapidly and involve the renal parenchyma to such an extent that the term primary contracted kidney is warranted. In young individuals with a very high diastolic blood pressure a necrotizing arteriolosclerosis may develop. Ten per cent. of the deaths in essential hypertension are due to renal involvement.

Renal Function

Renal function is, as a rule, normal or only slightly diminished. Renal function may be progressively impaired, if the kidneys

become sclerosed and a primary contracted kidney develops. A necrotizing renal arteriolosclerosis will result in a very sudden and marked curtailment of the kidneys' activities and is followed by death from retention uremia.

Edema

Edema is absent, unless it is brought on by myocardial insufficiency.

Anemia

Anemia is not present, as a rule. A high normal or a polycythemic blood count is characteristic of the cases with a tendency to cerebral involvement. If renal function is impaired because of the development of a primary contracted kidney, a progressive anemia will be found.

Uremia

The uremia of renal insufficiency comes on slowly with the formation of a primary contracted kidney, or rapidly, if there is a renal necrotizing arteriolosclerosis. The uremia of cerebral arteriosclerosis occurs frequently.

Disturbances Associated with Acute Diffuse Glomerular Nephritis

(Acute nephritis, acute glomerular nephritis, intracapillary glomerulitis)

Cause

An infection with the hemolytic streptococcus produces toxins which affect the capillaries throughout the body resulting in a universal capillaritis; the kidneys, the subcutaneous tissues and the central nervous system give clinical evidence of such an

invasion through nephritis, edema and uremia. While the evidence that hemolytic streptococcus toxins are the cause for the syndrome accompanying acute diffuse glomerular nephritis is not conclusive, yet all researches on this subject during the last decade indicate that this is probably the real etiological agent.

Pathology

Kidneys. — As the name of this form of nephritis signifies, virtually all of the glomeruli are involved.

Albuminuria. — The amount of the albumin in the urine may be slight, or it may be marked. The progress of the disease usually is gauged by the quantity of albumin in the urine. This is one of the most available guides for diagnosis and therapy, but its reliability for finer interpretations is open to question. As the renal lesion heals, the albuminuria may be of the orthostatic type, that is, albumin may be present in the urine while the patient is in the erect posture and disappear or be reduced to a mere trace, when he lies down.

Hematuria is found almost constantly though it may have to be demonstrated by the microscope. Frequently the urine is markedly blood stained on gross examination. This is one of the important diagnostic features of acute diffuse glomerular nephritis.

Blood casts are supposed to be pathognomonic of this type of nephritis.

Heart. — The heart usually shows no noteworthy changes. There may be acute dilatation followed by a myocardinal insufficiency. This has been ascribed to the strain imposed by the hypertension, but it is probably due to the degenerative effect of the hemolytic streptococcus toxins upon the heart muscle.

Retina. — There are no changes in the eye grounds even when amaurosis is present.

Blood Pressure

Hypertension develops at some time in the course of the nephritis. It usually subsides rapidly and may exist only for a day or two. On this account it may escape observation. Great stress has been laid upon a rise of blood pressure as a differential diagnostic point between diffuse glomerular nephritis and focal glomerular and tubular nephritis. This rule is subject to exceptions and must be interpreted cautiously. The height of the blood pressure varies greatly; it may be slight, or it may be marked, reaching well over 200 mm. of mercury. Both the systolic and the diastolic readings are elevated.

Renal Function

Oliguria is the rule; there may be anuria. The characteristics of the impairment of renal function in acute diffuse glomerular nephritis are oliguria, a very high urinary specific gravity, a diminished output of sodium chloride and a moderate or no increase in the blood urea. The oliguria has a distinct tendency to correct itself, and many of the favorable results of special forms of treatment may be attributed to the spontaneous resumption of elimination of urine by the kidney.

Edema

Although edema is considered one of the important signs of acute diffuse glomerular nephritis, often it is lacking. Many cases, in which no edema develops, escape recognition, and only when an albuminuria is discovered in later years is it realized that an acute diffuse glomerular nephritis must have existed at

some previous time. The edema may be absent, may be moderate in intensity affecting the subcutaneous tissues only, or it may be very marked with involvement of the body cavities constituting an anasarca. The cause for the edema is supposed to be two-fold, first the diminished amount of water eliminated in the urine and second the diffuse capillaritis, the generalized disease of the capillaries, effected by the toxins produced by the hemolytic streptococcus. The edema here has an entirely different etiology from that accompanying tubular nephritis. The latter is brought on by a lowering of the blood albumin and a consequent diminished osmotic pressure within the blood. In acute diffuse glomerular nephritis the latter form of edema may be found at times and is then often designated as a "nephrotic component".

Anemia

The hematuria, the albuminuria, the edema, the effect of the original infection, the low protein diet and the renal insufficiency all contribute to a loss of hemoglobin and red blood cells. However, the disease usually is of such short duration that these factors do not have an opportunity to exert their influence, and consequently anemia is rarely found.

Uremia

The uremia of acute diffuse glomerular nephritis (sthenic, convulsive or epileptiform uremia) is present in many cases.

Disturbances Associated with Subacute Diffuse Glomerular Nephritis

(Extra capillary glomerulitis, fulminating glomerular nephritis, "sturmischer Typus" of Löhlein)

Pathology

Kidneys. — The pathological process in the kidneys is a continuation of that of acute diffuse glomerular nephritis. The characteristic lesion consists in the formation of an exudate and a proliferation of epithelial cells within the extra capillary space (that is, in the space between the glomerular tuft and Bowman's capsule), which gradually compress and finally obliterate many of the glomerular tufts.

Hematuria, present in the acute stage, disappears in the subacute stage, as the circulation through the glomerular capillaries is shut off.

Renal Function

A progressive diminution in kidney activity and a change in the type of impairment of renal function from that found in acute diffuse glomerular nephritis is the most important feature in making a diagnosis of the advent of subacute diffuse glomerular nephritis. The specific gravity becomes low and fixed at a level of 1.010; the oliguria often persists; there is a marked and progressive rise in the blood urea and the other non-protein nitrogenous constitutents of the blood.

Edema

Edema usually is present. This is the same form of edema that occurs in acute diffuse glomerular nephritis.

Anemia

The marked renal insufficiency, prolonged albuminuria and low food intake are responsible for the development of a distinct secondary anemia.

Blood Pressure

In many instances there is a moderate hypertension. In some cases the blood pressure is at a more or less normal level, presumably because of the weakened condition of the heart, arteries and general musculature.

Uremia

The uremia of renal insufficiency terminates life within a few weeks to five months after the onset of this form of nephritis.

Disturbances Associated with Chronic Diffuse Glomerular Nephritis

(Chronic diffuse nephritis, chronic glomerular nephritis, chronic interstitial nephritis, secondary contracted kidney)

Pathology

The signs, symptoms and pathology are those of acute nephritis with the exception that the uremia of acute diffuse glomerular nephritis does not occur. When an acute exacerbation of the chronic nephritis develops, that is, when there is a complicating acute diffuse glomerular nephritis, then all the disturbances, including uremia, characteristic of the acute type of nephritis, or more accurately, of a hemolytic streptococcus toxin affection, may become evident.

Kidneys. — The lesions in the kidneys may continue more or less as in the acute form, or they may progress with formation of fibrous tissue and development of a secondary contracted kidney, or they may heal, and all signs of nephritis disappear. From the clinical point of view, these stages are recognized by

calling the earlier periods of the kidney involvement, when renal function is good, the compensated stage, and the later periods, when kidney activity is curtailed, the decompensated stage. The result of the progress of the disease in the kidneys is that the clinical picture is not necessarily fixed, nor one that is consistently or systematically progressive, but one that is full of surprises, if a clinical survey of the case is not made at frequent intervals.

Retina. — The eye grounds may be normal. If hypertension has existed for some time, there may be an albuminuric retinitis.

The *heart* is normal except where a prolonged elevation of the blood pressure causes hypertrophy, dilatation and finally cardiac failure similar to that found in essential hypertension and described elsewhere in this volume.

Albuminuria varies a great deal. It may be slight, or it may be very marked. As the kidney becomes fibrosed and a secondary contracted kidney develops, the albumin in the urine frequently is reduced to traces and may disappear entirely. A diminution or even a cessation of the albuminuria would, under these circumstances, be a poor prognostic sign.

Hematuria and *blood casts* may continue indefinitely after the acute stage has passed. It is supposed that as the inflammation of the glomeruli subsides, the hematuria diminishes and subsequently ceases. A reappearance of the blood and red blood cell casts in the urine points to a complicating acute diffuse glomerular nephritis, that is, an acute exacerbation of the chronic nephritis.

Renal Function

The same deviations from the normal are found in the chronic as in the acute form of diffuse glomerular nephritis.

That is, the concentration of the urine is excellent, there is a fixation of the specific gravity at a high level, the volume of urine is diminished, and the blood chemistry is normal or moderately elevated. These disturbances in the activities of the kidney may last a few days, may extend over a period of months, or may cease entirely, to return at a later date, or remain in abeyance indefinitely. The intermittent appearance and disappearance of the oliguria and the concomitant disturbances in renal function are characteristic of chronic diffuse glomerular nephritis in the compensated stage.

When the kidney becomes fibrosed and the stage of secondary contracted kidney is reached, the oliguria gradually changes to polyuria, the specific gravity becomes low and fixed, the values for urea and the other non-protein nitrogenous constituents of the blood rise, and the progress of events, that terminate in the uremia of renal insufficiency, has begun.

Edema

The edema in chronic diffuse glomerular nephritis parallels the oliguria and the associated diminished elimination of salt in the urine very closely. Like the disturbance of renal function, it is very likely to be intermittent. The nephrotic component (hypoalbuminemia and hypercholesterolemia) may be present, as it is in acute diffuse glomerular nephritis. The edema may be slight or severe; a marked anasarca is often found. With the advent of the polyuria, accompanying the change of the renal lesion to that of secondary contracted kidney, the edema diminishes, as a rule, and may disappear completely. When cardiac insufficiency exists, the edema due to that disturbance naturally will be in evidence.

Anemia

Secondary anemia becomes marked if the type of impaired renal function that is associated with an accumulation of the non-protein nitrogenous constituents of the blood develops. A persistent albuminuria and a low protein diet are very likely to accentuate the loss of the hemoglobin and the red blood cells.

Blood Pressure

As a rule, there is hypertension in chronic diffuse glomerular nephritis. Both the systolic and the diastolic pressure are elevated. The arterial tension may be only slightly above the normal, or it may be very high, so that considerable doubt may exist as to whether the blood pressure or the nephritis was primary. All the sequelæ of a long maintained hypertension, as discussed under essential hypertension, may become manifest in the course of the chronic nephritis.

Uremia

The uremia of acute diffuse glomerular nephritis may develop, if there is an acute exacerbation of the chronic nephritis. The typical form of uremia is that of renal insufficiency which accompanies the curtailment of kidney activity in the decompensated stage of chronic diffuse glomerular nephritis. Retention uremia is the usual cause of death in this form of Bright's disease.

Disturbances Associated with Focal Infectious Glomerular Nephritis

(Focal hemorrhagic glomerular nephritis, focal non-embolic nephritis, infectious nephritis, hemorrhagic catarrh, benign hemorrhagic nephritis)

This lesion in the kidneys is signalized clinically by a hematuria which may occur in the course of any infectious disease. There are none of the other signs of Bright's disease, such as hypertension, edema, impairment of renal function or uremia. The hematuria usually disappears when the focus of infection, which is the cause of the kidney complication, clears up.

Disturbances Associated with Focal Embolic Glomerular Nephritis

(Embolic nephritis, embolic hemorrhagic nephritis, embolic non-suppurative focal nephritis, embolic glomerular lesions of sub-acute bacterial endocarditis, multiple glomerular embolization)

Pathology

Kidneys. — Bacterial emboli originating from the heart valves in subacute infectious (bacterial or malignant) endocarditis, which lodge in some of the glomeruli, are responsible for this renal affection. The causal disease almost invariably persists to terminate fatally, and the nephritis, once it has begun, usually does not heal but is kept up by a continuous series of emboli. In some instances, when a very large number of glomeruli are involved, the morphological changes in the kidney are similar to those of subacute diffuse glomerular nephritis and bring about death through the uremia of renal insufficiency.

Hematuria is an important diagnostic sign. The presence of even a moderate number of red blood cells in the urine of cases of malignant endocarditis points to the existence of a focal embolic glomerular nephritis.

Renal Function

This is normal except in the occasional instance when a subacute diffuse glomerular nephritis develops. Impairment of renal function, especially a low fixed specific gravity and an elevation of the blood urea, are the most readily available signs by which a complicating subacute form of nephritis can be recognized.

Edema

Edema is absent.

Anemia

A secondary anemia is a characteristic accompaniment of malignant endocarditis. There is rarely sufficient hematuria or albuminuria due to the focal embolic glomerular nephritis itself to bring about a significant reduction in the hemoglobin or red blood cells.

Blood Pressure

The blood pressure is normal.

Uremia

There is no uremia except occasionally when the renal lesion changes to that of a subacute diffuse glomerular nephritis. If this occurs, the uremia of renal insufficiency follows and causes death.

Disturbances Associated with Albuminuric Tubular Nephritis

(Febrile albuminuria)

There is a degenerative change in the tubules of the kidney. The only sign of renal involvement is an albuminuria. The albuminuria clears up, and the kidney lesions heal when the infectious disease, which causes the irritation of the kidneys, is cured. It is very necessary when observing cases of febrile albuminuria during the course of a pneumonia, a tonsillitis or other infection, to bear in mind that what at first thought is believed to be an albuminuric tubular nephritis may in reality be an acute diffuse glomerular nephritis. The differentiation is at times extremely difficult. The desirability of distinguishing between the two conditions is obvious. The presence of a hematuria during the course of the fever and the persistence of the albuminuria after the temperature has returned to normal are indications of glomerular involvement.

Disturbances Associated with Anuric Tubular Nephritis

(Bichloride of mercury poisoning)

Pathology

Kidneys. — There is an advanced degree of degeneration of the epithelium lining the tubules. The tubular epithelium regenerates, and the renal lesions heal completely, provided the patient survives the poisoning by bichloride of mercury.

Intestines. — The mercury irritates the mucous membrane of the stomach and of the large intestines, often resulting in a hemorrhagic gastritis and colitis.

Albuminuria is marked provided any urine is eliminated.

Renal Function

A marked oliguria rapidly progressing to anuria is characteristic. The urea and other non-protein nitrogenous substances in the blood accumulate very quickly and reach high values. An unexplained diminution in the sodium chloride content of the blood usually occurs. If the urine flow is re-established, the patient recovers.

Edema

There is puffiness about the face and of all the subcutaneous tissues, but no accumulation of large amounts of fluid.

Anemia

This form of nephritis does not persist long enough to result in a definite secondary anemia.

Blood Pressure

Although there is a marked renal insufficiency, the blood pressure does not rise a great deal. The arterial tension often remains normal. A systolic pressure of 160 to 170 mm. of mercury is very high for this form of nephritis. During the last few days of life, in fatal cases, the blood pressure returns to an approximately normal level, if it was increased at an earlier period.

Uremia

The uremia of renal insufficiency is present. If the elimination of urine is not resumed, the outcome is fatal.

Disturbances Associated with Edematous Tubular Nephritis

(Lipoid nephrosis, genuine nephrosis, chronic nephrosis, diabetes albuminuricus)

Pathology

Kidneys. — On gross examination the kidneys often have yellowish color indicating the presence of double refractile lipoids. On microscopical examination the albuminous, hyaline and necrotic degeneration of the tubular epithelium, one or all, may be in evidence; double refractile fat globules in the basal portion of these epithelial cells are often found. The glomeruli, according to some authors, show the lesions usually ascribed to acute diffuse glomerular nephritis, though these are not marked, and are claimed by other investigators to be lacking in typical instances of the disease. Necrosis of the tubular cel's is usually followed by regeneration. In some cases a sclerosis of the necrotic cells occurs instead and initiates the changes which result in the formation of a secondary contracted kidney.

Lipoid materia 's not only deposited in the kidneys, but also in the liver, the suprarenal glands, the lymph nodes, the spleen and probably in most of the soft tissues. This indicates that this form of Bright's disease is not originated by the lesions in the kidneys but is a constitutional disorder.

Thyroid gland. — There are degenerative changes indicative of exhaustion caused by excessive functional activity.

Basal Metabolism. — In some, but not in all, cases of edematous tubular nephritis there is a low basal metabolic rate. This has been ascribed to one of two causes: first to deficient activity of the thyroid gland; second, to the increased weight, incident to

the edematous accumulations of inert fluid, which gives the calculations for the metabolic rate false values. Both of these explanations deserve consideration. In this connection it is worth recalling the fact that in some instances of edematous tubular nephritis huge doses of thyroid substance may aid in the elimination of the edema.

Liver. — Atrophy and degeneration of the liver have been demonstrated. These lesions, like those in the thyroid, are attributed to the strain of functional overactivity.

Retina. — The eye grounds are normal.

Albuminuria. — A large amount of protein is eliminated in the urine. This suggests an abnormal permeability of the glomerular capillaries to the blood proteins. The cause of the albuminuria may be in the blood vessels themselves, or it may be the result of changes in the character of the proteins, or it may be brought about by other influences that have not been considered seriously thus far.

Hematuria is not found in typical cases of edematous tubular nephritis. The presence of red blood cells in the urine is regarded as conclusive evidence of glomerular involvement.

Blood Proteins. — There is a marked diminution of albumin and a tendency for the globulin to rise. This reverses the albumin-globulin ratio. The normal values are: albumin 4.7, globulin 2.7, total protein 7.4 grams per 100 c.c. of blood and the albumin-globulin ratio 1.7. In edematous tubular nephritis these figures may be regarded as typical: albumin 0.5, globulin 3.5, total protein 4.0 grams per 100 c.c. of blood and the albumin-globulin ratio 0.13 (table 31, Chapter XI). The osmotic disturbances caused by the diminution in the blood albumin are supposed to be responsible for the edema.

According to some authorities there may be a qualitative

as well as a quantitative change in the blood proteins. If this is the case, the newly formed material would act as a foreign protein and promptly pass through the glomerular capillaries into the urine. This theory accounts for the albuminuria and ascribes the starting point of the symptom complex of edematous tubular nephritis or genuine nephrosis to a primary change in the blood proteins. In an attempt to describe such sequence of events Epstein has termed this form of Bright's disease, diabetes albuminuricus.

Blood Cholesterol — There is a distinct cholesterolemia. The cholesterol values in edematous tubular nephritis range from about 300 to 1200 mg. per 100 c.c. of blood. The rise in cholesterol is ascribed to an effort on the part of the body to compensate for the loss of osmotic power created by the diminution in blood albumin.

Infection of the Peritoneum. — Recurring infections of the ascitic fluid with the pneumococcus or the hemolytic streptococcus are frequent. The susceptibility of the patient with edematous tubular nephritis to these bacterial invasions and his ability to recover from them are very remarkable. After several attacks of peritonitis have been overcome successfully, there usually is one which proves fatal.

Renal Function

Deviations from normal renal function in edematous tubular nephritis are incident to the formation and loss of edema. There is oliguria, a high, fixed specific gravity, a low concentration of salt and a high concentration of urea in the urine, while fluid is retained; when the edematous fluid is being eliminated, the specific gravity assumes a lower level, and the concentration of salt in the urine increases. There is no retention of urea in

this condition, and the values for the various non-protein nitrogenous constituents of the blood are within normal limits. Polyuria, a low specific gravity and an elevation of the blood urea are found, if the kidneys become sclerosed, and a secondary contracted kidney develops. This occurs infrequently, but it has to be kept in mind.

Edema

This is the characteristic sign of edematous tubular nephritis. It is often extreme. There are large amounts of fluid in the subcutaneous tissues and in the peritoneal cavities. The edematous accumulations are, as a rule, less marked in the pleural spaces. The edema accompanying this form of nephritis is now believed to be the result of the diminished osmotic pressure of the blood colloids. The loss of albumin in the urine accounts for the marked lowering of the total protein and the albumin content of the blood. The diminution of these colloids in the blood lowers the osmotic tension within the vascular system and thus favors the retention of fluid in the extra-circulatory tissues and spaces. The functional pathology of the edema in edematous tubular nephritis differs widely from that of the edema occurring in acute or chronic diffuse glomerular nephritis or from that developing under the influence of myocardial insufficiency.

Anemia

In most cases of uncomplicated edematous tubular nephritis there is no secondary anemia. If a wasting disease, such as lues or carcinoma, is associated with the nephritis, there may be a drop in the percentage of hemoglobin and the number of red blood cells. Most instances of edematous tubular nephritis

that show a secondary anemia are those in which a diffuse sclerosis has begun and in which there is a progressive impairment of renal function.

Blood Pressure

This is usually maintained at a normal level in edematous tubular nephritis. An absence of any rise in blood pressure is regarded by many clinicians as one of the important indications that only the tubules and not the glomeruli are diseased. However, in some cases, in which the tubules only were shown to be involved and the glomeruli apparently intact on pathological examination, there had been a considerable elevation of the arterial tension during life. A systolic pressure as high as 175 mm. of mercury has been noted in such patients.

Uremia

Uremia is absent in edematous tubular nephritis. The uremia of renal insufficiency is found in those comparatively rare instances in which there is a far advanced sclerosis of the renal parenchyma, that is, a secondary contracted kidney.

Disturbances Associated with Hypertensive and Convulsive Tubular Nephritis

This is the type of nephritis which goes far to show that the constitutional signs of Bright's disease are not dependent upon the pathology of the kidney. The theories concerning the production of hypertension through glomerular involvement, that have been so painstakingly pieced together, fail to account for the marked rise of blood pressure that is found in the toxemia of pregnancy in which a distinctly tubular form of nephritis is present. It is only necessary at this point to state

that a tubular nephritis associated with convulsive seizures and hypertension may be caused by toxins elaborated in the course of pregnancy. For details of this syndrome, the reader is referred to monographs dealing with obstetrics.

Disturbances Associated with Arteriosclerotic Nephritis

(Primary involvement of the arteries and arterioles, vascular nephritis, benign nephrosclerosis, primary contracted kidney)

Pathology

Kidneys. — The lesions in the kidney may result from a persistent hypertension, in which case all the symptoms and signs of high blood pressure naturally are present. Reference is made to the summary of the findings in essential hypertension for an exposition of these facts.

Arteriosclerotic changes may occur in the absence of hypertensive disease. The spontaneous arteriosclerosis, which develops sooner or later with advancing years, may involve the kidneys to a disproportionate degree in comparison with the other organs of the body.

The renal vessels, especially the afferent glomerular arteries, become thickened, their lumen is narrowed and in advanced cases will be partially or completely obliterated. When the blood supply is no longer sufficient to support the corresponding renal unit, it atrophies and is replaced by connective tissue. The final result is a small, puckered kidney with very few surviving glomeruli which are functionally active. This constitutes the primary contracted kidney. While this advanced degree of renal fibrosis may develop rapidly, that is, within about a year after the process begins, it usually progresses much more slowly

and in fact is so gradual in its evolution that death usually occurs from some other cause before renal insufficiency closes the picture.

Albuminuria. — Only traces of protein are found in the urine.

Hematuria is absent.

Retina. — The eye grounds show the lesions incidental to arteriosclerosis. When hypertension exists, there may be a marked retinitis.

Renal Function

This is normal in the early stages. Impairment of renal function manifests itself in direct proportion to the number of glomeruli that undergo sclerosis. The urinary specific gravity has a tendency to become low and fixed at a level of 1.010, and the non-protein nitrogenous constituents of the blood gradually increase.

Edema

Edema is absent.

Anemia

Anemia is not present unless renal function is impaired, when there will be a diminution in the hemoglobin and the red blood cells in direct proportion to the degree of reduced efficiency of the kidneys.

Uremia

There are no signs of uremia until an advanced degree of primary contracted kidney develops, when the uremia of renal insufficiency will manifest itself.

Disturbances Associated with Arteriolonecrotic Nephritis

(Malignant nephrosclerosis, necrotic arteriolar nephrosclerosis, chronic hypertension with acute uremia)

Pathology

Kidneys. — There are multiple hemorrhages on gross examination. These are an indication of the severity of the vascular lesions. Arteriolonecrosis, endarteritis and periarteritis are found in many of the arteries and arterioles of the renal parenchyma. A necrotizing arteriolitis of the afferent glomerular arterioles is the essential lesion. This, by shutting off the blood flow to the glomeruli, renders them functionless and destroys them.

Pancreas, Spleen and Other Tissues. — Vascular lesions similar to those described in the kidney have been demonstrated in other tissues of the body. This indicates that the disorder is of extra-renal origin and that the kidneys are affected in the same manner as the other organs.

Hematuria comes on suddenly, and blood usually is present in the urine in considerable amounts.

Albuminuria. — A distinct albuminuria accompanies the hematuria.

Heart, Retina, Brain, Kidneys. — These are grouped in one section because they all show the pathological changes incidental to essential hypertension, and reference is made to that section for a summary of the lesions in these tissues. Arteriolonecrotic nephritis develops in patients, who have been afflicted with a marked and prolonged elevation of blood pressure, especially the diastolic pressure. This explains why

in this disease the pathological changes, the signs and the symptoms are those of arteriolonecrotic nephritis superimposed upon those of essential hypertension.

Renal Function

As the rapid destruction of the glomeruli takes place, there is a corresponding diminution in the activity of the kidney. There is oliguria, a low, fixed urinary specific gravity, a deficient elimination of solids ordinarily excreted in the urine and a mounting concentration of urea and other non-protein nitrogenous substances in the blood. The signs, upon which the diagnosis of arteriolonecrotic nephritis mainly depends, are a rise in the blood chemistry and a hematuria which appear in a hypertensive patient of 50 years or younger.

Edema

Edema is absent unless it is the result of myocardial insufficiency.

Anemia

The duration of this disease is too short for the hematuria and the impairment of renal function to bring about a secondary anemia.

Blood Pressure

There is a pre-existing marked elevation of both the systolic and the diastolic blood pressure. The strain imposed by such a hypertension over a long period is probably responsible for the necrotic and inflammatory lesions of the arteries and arterioles throughout the body. The arteriolonecrotic nephritis is a part of this generalized disease.

Uremia

The uremia of renal insufficiency develops when a large number of the glomeruli are destroyed and cease to function. A fatal termination due to the uremia of renal insufficiency occurs in about a month, more or less, after the first signs of the arteriolonecrotic nephritis appear.

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